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Original Communications

TETRALOGY OF FALLOT

ANALYSIS OF FORTY-ONE CASES OF PATIENTS TREATED SURGICALLY AT THE UNIVERSITY OF MINNESOTA HOSPITALS

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AT one time the achievement of the proper diagnosis of congenital abnormalities of the heart was of almost purely academic interest, serving little practical purpose other than to aid in the evaluation of prognosis in individual cases. Aside from its usefulness in differentiating such abnormalities from rheumatic carditis, its value to the patient was usually minimal. At present, however, as a result of notable advances in the surgical treatment of various types of congenital cardiac defect, added responsibility is placed on the physician, especially the pediatrician, to recognize their presence. The correct diagnosis is as important to the patient in terms of definitive treatment as identification of the causative microorganism is in an infectious disease. Increased interest in the problem of diagnosis has led to the development of a variety of special clinical techniques such as cardiac catheterization and roentgen ray studies following injection of contrast media, which furnish valuable confirmatory data.

Since the presentation in 1945 of a successful method for the surgical treatment of patients with tetralogy of Fallot by Blalock and Taussig,[7] the correct diagnosis of this abnormality has become especially important. Concentration of interest on the subject has served to advance our knowledge regarding all types of congenital malformations of the heart.

The purpose of the present communication is to review the diagnostic findings and the results of treatment by means of the Blalock-Taussig procedure in forty-one tetralogy patients who were admitted to the University of Minnesota Hospital between September, 1946, and December, 1947. In four of these the thoracotomy was exploratory in character, no attempt being made to carry out the anastomosis; two patients expired during surgery, and the remaining thirty-five had the systemic-pulmonary arterial shunt constructed. The ages of the patients ranged from 18 months to 37 years, the

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All surgical Operations were performed by Dr. John R. Paine and Dr. Richard Varco of the Department of Surgery. A report of thier surgical experience will be published elsewhere.

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majority being between 6 and 8 years. The average age was 8.8 years. Four patients were 16 years of age. The operation was carried out on three of these.

ANATOMIC AND PHYSIOLOGIC CHARACTERISTICS OF TETRALOGY OF FALLOT

The tetralogy of Fallot consists of the following four abnormalities: (1) pulmonary stenosis with narrowing of the opening between the ventricle proper and the infundibulum; (2) interventricular septal defect; (3) dextroposition (with over-riding) of the aorta; and (4) right ventricular enlargement. The resulting symptoms of such abnormalities, namely, a high degree of cyanosis, dyspnea, faintness, possibly syncope, clubbing of the digits, polycythemia, and an increased oxygen capacity of the blood, occur in varying degrees.

CLINICAL HISTORY

Cyanosis is sometimes not present at birth, being noted first either at the time when the ductus arteriosus closes or when a relatively mild pulmonary or upper respiratory infection occurs during infancy; or it may not be noted until the activity of the patient is increased, for example, when he begins to creep. The ductus arteriosus is normally completely closed by the third month, although there is constriction or functional closure immediately after birth.[22] Closure may be delayed even further and the duct may even remain patent. There may be reopening of the duct later in life. Why the ductus should close when it is a functioning structure is not known. Barklay and Salmon[3] report that two out of ten operated patients were found to have a small open duct present. We have seen two patients, both about 3 years of age, in whom a machinery type murmur was found to have developed. Surgery was postponed in these cases until proper evaluation could be made as to the efficiency of the ductus in compensating for the defect. This observation should lead one to postpone surgery until the age of 3 years, if possible, so that any such compensatory attempts on the part of the body may be given an opportunity to be recognized. In the patients presented here, the onset of cyanosis was noted between the time of birth and 5 months in twenty-one cases (51.2 per cent); between 6 months and 2 years in fifteen cases (36.6 per cent); between 3 and 7 years in three cases (7.3 per cent); and two cases (4.9 per cent) the onset of cyanosis was uncertain (Table I).

Physical endurance was restricted in varying degrees, the distance which the patient could walk on level ground being used as a good clinical index. Eighteen (43.9 per cent) of our patients could walk less than one city block; fifteen patients (36.6 per cent) could walk from one to two blocks without exhaustion; five patients (12.1 per cent) had an endurance of three to six blocks; two patients (4.9 per cent) could go from seven blocks to one mile; and one patient (2.5 per cent) was able to walk more than one mile. Whether or not the patient suddenly feels exhausted and "squats" down in his tracks or feels fatigued but can walk into shelter or to a chair are also good indices.

TABLE I. SUMMARY OF CLINICAL HISTORIES AND PHYSICAL STATUS

HISTORY OR STATUS	%
Cyanosis first observed	
Birth to 5 months	51.2
6 months to 2 years	36.6
3 years to 7 years	7.3
Indefinite	4.9
Physical endurance (walking)	
Less than 1 city block	43.9
1 to 2 blocks	36.6
3 to 6 blocks	12.1
7 blocks to 1 mile	4.9
More than 1 mile	2.5
History of syncope or convulsions on exertion	36.6
Physical development	
Good	43.9
Fair	43.9
Poor	12.1
Occurrence of right aortic arch	21.9
Heart size	
Normal	41.5
Slightly enlarged	34.1
Moderately enlarged	4.9
Small	19.5

Syncope (or a convulsion) frequently occurs in those severely taxed. Fifteen of our patients (36.6 per cent) experienced this type of symptom. Seven of the ten patients studied by Barklay and Salmon[3] had episodes of syncope. The patient's unwillingness to tolerate anything which interferes with free breathing such as thumb-sucking, removal of clothing over the head, washing the face, or blowing the nose, is an indication of his previous experience with and fear of the sensation of suffocation.

PHYSICAL EXAMINATION

The patient is sometimes undersized and may be somewhat emaciated. The degree of retardation in physical development corresponds approximately with the degree of circulatory deficiency. In the present study development was found to be "good" in eighteen patients (43.9 per cent), "fair" in eighteen (43.9 per cent) and "poor" in five (12.1 per cent). In our patients the degrees of cyanosis and clubbing of the digits were found to be directly related to the severity of the disease. Spinal kyphosis was frequently present.

The patient is usually very apprehensive, the smaller children showing complete dependence upon the parents. The aortic second sound in a small child is clearly audible in the second left interspace and may be interpreted as the pulmonic second sound. A normal sinus arrhythmia is the rule. Heart block occasionally results from the septal defect. This condition was not observed in any of our patients. The blood pressure is usually within normal limits, sometimes slightly low. The pulse pressures found here varied from 10 to 50 mm. of mercury, most frequently being between 20 and 30 mm. There is no unusual relationship between that of the arms and that of the legs. It is frequently very difficult to obtain the blood pressure, particularly the diastolic. The reason for this is obscure. Olin and Hughes[16] found a very much elevated blood pressure in one of their two cases. Signs of embolism, cerebral or peripheral, were noted in three instances in the present series.

ROENTGEN EXAMINATION

On fluoroscopy the heart shadow is found to be somewhat widened, especially to the left, without marked cardiac enlargement. Of our cases, the heart size was found to be normal in seventeen patients (41.5 per cent), slightly enlarged in fourteen (34.1 per cent), more markedly enlarged in two (4.9 per cent), and small in eight (19.5 per cent). Unfortunately, the characteristic boot shape was not always obvious. As a result of the right ventricular enlargement a bifid apex may be seen with the notching at the apex indicating the right ventricle below and the left above, the pulsations in each being visible.

Although the arch of the aorta usually descends on the left side, it has been demonstrated that it descends on the right side in about one-fifth of the cases.[23] Nine of our patients (21.9 per cent) showed this abnormality. The importance of this lies in the fact that, since the innominate artery always lies on the side opposite to that on which the aorta descends, the side on which the incision for surgery may be made will depend upon where the vessel to be used for anastomosis lies. Thirty-two of the thirty-five anastomoses completed in our series of cases were made between the right or left subclavian artery and the right or left pulmonary artery, respectively. The innominate artery was used in but three cases.

Because of the decrease in pulmonary circulation, the pulmonary markings are found to be less marked than normal. Although not all of the patients in this series showed a high degree of decrease in the peripheral vascular pulmonary markings, every one showed some decrease in the size of the hilar vessels. The other important positive criterion is a small pulmonary artery and conus. We have found the decrease in pulsations of these vessels to be of more diagnostic aid than is the decrease in vascular markings, since the latter may sometimes be equivocal.

SPECIAL LABORATORY DATA

Laboratory findings are significant only in so far as they are characteristic of the disease and if they change in the postoperative state. A polycythemia was invariably present in these patients, the degree being roughly parallel to the degree of cyanosis and of hypoxemia. It has been found that, in contrast to the maintenance of a normal relationship between the volume of red cells and the volume of the plasma in polycythemia vera, the volume of the plasma in cases of cyanotic heart disease has been found to be below the expected level,[9] thus increasing the oxygen-carrying capacity of the blood at the price of increased viscosity. (Table II.)

TABLE II. SUMMARY OF DATA REGARDING BLOOD

	HEMOGLOBIN (GM. PER 100 C.C. BLOOD)	ERYTHROCYTES (MILLIONS PER CU.MM. BLOOD)	HEMATOCRIT (% R. B. C.)	OXYGEN SATURATION OF ARTERIAL BLOOD (%)
Preoperative	12.6-25.6	5.7-12.6	50-85	15.3-86.8
Postoperative	11.1-21.6	3.5-10.7	37-75	21.2-90.9

Taussig states that, in children, as long as the oxygen saturation of the arterial blood remains above 66 per cent, there is no need for and consequently is no stimulus leading to polycythemia.[22] We have not always found this to be true in our series. However, we have found it true that the hematocrit reading tends to be lower in those patients with the higher oxygen saturation values. The preoperative hemoglobin values in our group varied from 12.6 to 25.6 Gm. per 100 c.c.; postoperatively they ranged from 11.1 to 21.6 Gm. (See Table II.) This represented a decrease of 0.5 to 9 Gm. in all of the cases studied and a decrease of from 1.9 to 9 Gm. in those with a good result, the average decrease of about 4 Gm. resulting.

The erythrocyte count preoperatively was found to be between 5.67 and 12.6 millions per cubic millimeter; postoperatively between 3.5 and 10.7. This represents a decrease of 0.2 to 4.6 million cells per cubic millimeter in all the patients and of 0.6 to 4.6 in those with a good result from operation, the average fall being about two million. The preoperative hematocrit values were found to be between 50 and 85 per cent, whereas postoperatively they were between 37 and 75 per cent. A decrease in reading of 4 to 20 per cent was found in all of the cases and of 6 to 20 per cent in those with good results, the average fall being about 13 per cent. The decreases in hemoglobin and hematocrit values occur more rapidly (one to three weeks) than the fall in the erythrocyte count, which takes from one to three months. This is in contrast to changes in the degree of oxygen saturation of the arterial blood, which changes almost immediately after establishment of the anastomosis.

Oxygen saturation studies are made both before and after surgery. This gives comparable results if the patient is under basal conditions. Therefore, the patient is given a relatively short anesthetic of Baird's solution (Pentothal Sodium and curare) rectally and intravenously when the arterial blood is drawn to prevent struggling and crying. The blood is obtained from the femoral artery. The method most commonly used for determining the oxygen content is that of Van Slyke.[18] As will be noted later, evaluation of the exercise tolerance shows indications of being much more accurate. Since the degree of oxygen saturation decreases with voluntary exertion or crying, evaluation of exercise tolerance has been found to be easier from a mechanical standpoint and also to be more reliable.

In our series, preoperative oxygen saturation values of 15.35 to 86.8 per cent were found. Postoperative values of 21.2 to 90.9 per cent were found. Changes varied from −0.7 to +54.9 per cent in all patients having thoracotomies and between +1.2 and +54.9 per cent in those patients in whom a good result was obtained, the average change being from +10 to +25 per cent. In Taussig's[22] series, the oxygen saturation values preoperatively were as low as 13 per cent and as high as 75 per cent and rose postoperatively to as much as 77 per cent, the majority of rises being from 20 to 50 per cent. The conditions under which these values were obtained, however, are unknown to us. In the cases of Barklay and Salmon[3] the average preoperative arterial oxygen saturation was 56.4 per cent; the average obtained postoperatively

was 80 per cent. The saturation never rises to the normal range of 94 to 97 per cent because of the over-riding of the aorta, an abnormality which, of course, persists after surgery.

There is a rise in the degree of oxygen saturation when a patient is allowed to breathe a high concentration of oxygen at basal conditions due to an increased oxygen content but with no change in the oxygen capacity. Such studies have recently been carried out in our laboratory, both preoperatively and postoperatively, by having the patient breathe 100 per cent oxygen after a sample of arterial blood has been drawn for determination of the degree of saturation, changes being measured by use of the Milliken-Smaller oximeter which is to be described shortly. The time necessary for the maximum saturation is noted and either a second sample of arterial blood is drawn or the percentage increase is indicated by the oximeter readings is recorded. We have found increases of 6 per cent to 15 per cent, but as yet an insufficient number of cases have been studied in this manner to justify drawing final conclusions.

In studies carried out during the surgical procedure, the increase was noted immediately following establishment of a shunt. The saturation times in ten of the patients on whom the test was performed ranged in preoperative times from ten to fifteen minutes, the normal range being about three to four minutes.[11] Postoperatively the values were within normal limits. Studies on three of Blalock's patients six months, one year, and two years postoperatively, respectively, also showed normal saturation times, although oxygen saturation studies with reference to their exercise tolerance still showed some limitations.[11] Burwell[8] made the observation that the Eisenmenger's complex could be differentiated from the tetralogy of Fallot by the short saturation time in the former.

The Milliken-Smaller oximeter measures the oxygen content by recording electrically the varying photometric characteristics of the blood as determined by the relative contents of oxyhemoglobin and reduced hemoglobin as the blood flows through the lobe of the ear, the readings being obtained in terms of percentage change. The advantage of using this method of determining the degree of hypoxemia is that immediate and direct readings may be obtained under varying conditions as desired. Its use for this purpose has been reported elsewhere.[11]

At the present time studies are under way to determine the effects of a standard amount of treadmill exercise on the percentage oxygenation of the blood, thus providing a more accurate and statistically comparable record of exercise tolerance. Decreases in oxygen saturation are noted and the time necessary for return to the original values is recorded (saturation time). In ten normal subjects, increases of oxygen saturation of one to 5 per cent were noted following this exercise, while definite decreases occurred in cyanotic patients. Too few patients have been tested as yet, however, to justify drawing final conclusions. There is good reason to believe that the comparative change in exercise tolerance after operation is more closely correlated with the clinical improvement of the patient than is the change in oxygen saturation levels. Two of the three patients of Blalock referred to previously showed

a 5 per cent decrease in saturation with "extended exercise."[11] However, preoperative values were not obtained. One patient reported from the Lahey Clinic had an oxygen saturation value fifteen days postoperatively which had fallen 5 per cent and seventy-five days postoperatively it had risen only 2 per cent from the preoperative value, although the clinical improvement was good. With the same exercise each time, the drop in oxygen saturation after exercise decreased from a preoperative value of 21 per cent to 9 per cent and then to 2 per cent in fifteen and seventy-five days, respectively.[20]

The electrocardiogram typically shows a wide QRS amplitude, peaking of P and T waves, and marked right axis deviation. These abnormalities were present in all of our patients. Olin and Hughes[16] reported one patient who had electrocardiographic evidence of coronary insufficiency.

It has been the opinion of some observers that many children with cyanotic congenital heart disease are mentally retarded. Contrary to this assumption, we have been impressed by the good, and in some cases, unusually good mental development shown. Psychometric examination made by Miss Audrey Arcola, clinical psychologist for the Department of Pediatrics, on thirteen of our patients picked at random, showed the following intelligence evaluation: low average, 4; average, 5; slightly above average, 1; and superior, 3. The oxygen saturation values in the "low average" group ranged from 49.9 to 86.8 per cent; in the "average" from 43.5 to 75.8 per cent; in the patient "slightly above average," 84.0 per cent; and in the "superior" group from 65.2 to 79.37 per cent. No correlation between the result of the psychometric evaluation and the preoperative oxygen saturation levels could be found.

Comparison of values for vital capacity, venous pressure, blood volume, and circulation time may be useful, but too few patients in this series had these determinations made routinely to justify attempts at correlation. Such data as bleeding time and clotting time, carbon-dioxide combining power of the plasma, blood urea nitrogen, and blood chloride levels are obtained preoperatively, both for evaluating the patients' ability to undergo surgery and as a base line for postoperative care. Blood, as well as nose and throat cultures, are taken, and appropriate preoperative chemotherapy is given if necessary to insure aseptic conditions in so far as possible. Dental examination and the preoperative removal of loose teeth has proved a helpful precaution, penicillin being used before and after extraction.

REGARDING SURGERY

While detailed discussion of the surgical procedures employed to ameliorate the circulatory dysfunction in tetralogy of Fallot is quite beyond the scope of this paper, brief comment on certain aspects of the problem is not inappropriate. Obviously, the question regarding the likelihood of the patient's being benefited significantly by operation should be considered of prime importance in determining the advisability of this form of treatment. Clinical judgment concerning the need for operation and risks involved can be bolstered by information regarding the degree of oxygen saturation of the ar-

terial blood, the patient's exercise tolerance, and the differential arterial pressures as measured directly by means of vascular and cardiac catheterization.

Preoperative preparation of the patient is of paramount importance. Adequate hydration before operation tends to obviate the necessity of having to administer fluids intravenously later on. This decreases the danger of cardiac dilatation and decompensation which may arise secondary to the establishment of the new shunt. Penicillin is given prophylactically in large doses for forty-eight hours before surgery as well as postoperatively. This is given in order that the blood stream may be rendered as free as possible from pathogenic penicillin-sensitive microorganisms, since the surgical anastomosis presents a favorable site for bacteria to collect. The other routine preoperative medications are morphine and atrophine, the former being given in dosages indicated for the age. The atropine is given in relatively large but safe doses in order to depress the vagus nerve sufficiently to counteract its depressant effect on the heart when the latter is stimulated by unavoidable manipulation during the operation. The dosages in the present cases were 0.6 to 0.3 mg. for patients ranging in age from 6 to 13 years and 0.2 to 0.15 mg. for those patients who were younger than 6 years. Application of a local anesthetic to the vagus nerve at the time of surgery was used to magnify the effects of atropine.

The anesthetic found to be most satisfactory and the one which was used in the last twenty-six of our cases was the pentothal-curare solution described elsewhere by Dr. J. W. Baird[2] of the Division of Anesthesiology of the University of Minnesota. Administration of the solution is combined with intratracheal inhalation of 50 per cent nitrous oxide and oxygen. Cyclopropane and ether were used originally; however, four fatalities occurred under these inhalation anesthetics. To what extent anoxia or increased vagal stimulation accounted for these unfortunate results is not definitely known.

Since blood must flow after anastomosis from the systemic to the pulmonary circulation, operation is ineffective if the pressure in the latter system is too high. The maximum pulmonary arterial pressure used as a guide by the surgeons in our clinic has been that recommended by Blalock, namely, 30 cm. of citrate solution. In three of the cases reported here, however, the pressures were 31, 34, and 35 cm. of citrate solution, respectively. However, the results of operation on these patients were completely satisfactory. It is possible that the 30 cm. maximum pressure value can be revised upward for patients having systemic arterial pressures above certain levels.

POSTOPERATIVE CHANGES

A continuous murmur is usually heard postoperatively over the site of the anastomosis, sometimes appearing immediately following operation and at other times developing several days or weeks afterward. In nine of our patients it was first heard immediately postoperatively; in five it was heard later on the day of the operation. It was heard on the day following operation in three patients; on the third day in five; on the fourth in one; and on the fifth in two. In four other patients it was heard first on the sixth, seventh,

ninth, and twenty-first postoperative days, respectively. No murmur was heard postoperatively in seven patients. Of these, two had end-to-end anastomoses (one of the latter expired and the other had a result of questionable value) and three obtained no relief from their symptoms. The sixth patient in the group expired. The remaining one had a good result. Although the murmur is heard over the site of the anastomosis, it is often found to be louder in the back on that side. Occasionally, when no new murmur develops, the systolic murmur found previously is accentuated. The lack of a continuous murmur corresponds with the absence of a thrill over the anastomosis immediately after it is established. Even though a thrill is palpable below the clavicle after the chest has been closed, we have found that it may take some time for the murmur to develop.

The heart size increases in varying degree but not to an alarming extent. This increase is predominantly left ventricular. Although the enlargement begins almost immediately, the heart does not usually reach its maximal size until the end of the second week. Examinations as long as several months later in our cases showed no further increase in heart size. That the maximal degree of enlargement occurs almost immediately without change thereafter is not surprising. Lewis[13] has shown that prolonged overwork does not cause cardiac failure and Palmer[17] has demonstrated that cardiac enlargement in essential hypertension does not increase after the blood pressure has been stabilized. The vascularity of the lung field is moderately increased within a period of one to two weeks in most cases. The increase in the pulsations of the pulmonary vessels as seen on fluoroscopic examination is also indicative of the increase in pulmonary blood flow. The pulse pressures in our series of cases changed as a result of operation from −7 to +26 mm. of mercury, with an average of about 20 mm. increase. These changes are frequently not as great as might be expected with a shunt comparable with that in patent ductus arteriosus having been established. The changes show no constant relationship to the operative results.

COMPLICATIONS

In our experience *simple pleural effusion* was probably the most common postoperative complication encountered, the fluid occurring in significant amounts in 21 or 50 per cent of the patients. Thoracentesis for relief of respiratory embarrassment was required in three cases only. Cultures of the fluid removed were usually found to be sterile. One patient expired following removal of but 20 c.c. from a total of 1,900 c.c. of fluid in the chest. This death appeared to be due to a sudden shift of the mediastinum.

Chylothorax, occasionally resulting from damage to the thoracic duct when the left side of the chest is entered, is a more serious complication. It occurred in three patients in this series. All required repeated drainage. One was tapped seventeen times, yielding a total of 9.5 liters of fluid. While the mortality in general chest surgery complicated by chylothorax is stated to be as high as 50 per cent, all three of these patients survived.

The only therapeutic measure indicated in chylothorax other than thoracentesis and chemotherapy is that of maintaining normal levels of the various blood plasma constituents, such as proteins and electrolytes, by either the enteral or a parenteral route. *Hemothorax* occurred in two of our patients. One, which was massive and bilateral, was followed by death. The source of the hemorrhage was not adequately explained at autopsy, the anastomosis being unruptured.

Horner's syndrome was found to be present shortly after surgery in four of our patients, the pupil of the eye on the operated side being the smaller of the two. This complication is doubtless due to the fact that superior cervical ganglion fibers proceed craniad via the plexus surrounding the internal carotid artery. Although the one case reported from the University of Texas showed no return to normal,[3] ours did. One patient in our series showed ptosis and mitosis without changes in sweat secretion.

Hoarseness has been found to occur postoperatively by different observers. Although this may be the result of the intratracheal intubation only, it may also be the result of laryngeal or supraglottic edema, being sufficiently severe to require tracheotomy. This measure was necessary in one patient of the present series. Hoarseness may also be the result of temporary injury to the recurrent laryngeal nerve, should the latter take an aberrant course. Damage to the phrenic nerve is evidenced by diaphragmatic paralysis and by paradoxical diaphragmatic movement as demonstrated by fluoroscopy. This is also usually a temporary finding but is present in spite of the resorption of pleural fluid. We have observed the complication very frequently.

Hemiplegia may occur as a result of a deficient blood supply, especially if the innominate artery is used for the anastomosis. It may also be the result of an embolus. The hemiplegia may or may not be permanent. The arm on the side of the operative site remains cool for a varying period of time and it may be a matter of months before the temperature approximates that of the unoperated side, when a radial pulse may then become palpable. We had gangrene of the arm occur in one patient who later expired.

Other complications are less common. Empyema, mediastinal shift, pneumothorax, urinary tract infection, and prolonged lethargy each occurred but once among our cases. Thrombosis of the anastomosis occurred in one patient also and there was some question of its development in a second case. Cardiac decompensation was conspicuously absent in this series.

RESULTS OF OPERATION

The operative result was evaluated from both the clinical and laboratory standpoints, the patients' subjective improvement being included as an important criterion. A good result was obtained in twenty-six patients, or 74.3 per cent of those having anastomoses performed. One other patient obtained a fair result, two showed questionable results, and four showed no improvement. Of those having anastomoses completed, five died, giving a mortality of 12.1 per cent. The over-all mortality was 19.3 per cent, including deaths in patients who had exploratory thoracotomies without anastomoses and deaths

which occurred after the patient had been discharged from the hospital. Blalock and Taussig[20] had an over-all mortality of 21 per cent in their first 243 patients subjected to operation. Barklay and Salmon,[3] in ten patients, had an over-all mortality of 20 per cent. Six of their patients were "much improved." Murray[15] reported a mortality of only 7.3 per cent in 41 cases operated. His report does not elaborate on the types of patients or on procedures.

SUMMARY

The characteristic clinical, roentgenological, and laboratory findings in the tetralogy of Fallot type of congenital heart disease are discussed with particular reference to their occurrence in the patients studied at the University of Minnesota Hospital. Special attention is called to the use of the Milliken-Smaller oximeter for determining the arterial oxygen saturation with and without exercise both before and after operation for evaluation of the degree of circulatory improvement. The worth-whileness of using a standard exercise tolerance test as a method of determining the degree of work limitation both before and after operation is emphasized.

Advantages of using Baird's pentothal-curare solution for anesthesia and increased doses of atropine sulfate preoperatively, as well as local application of an anesthetic to the vagus nerve at the time of operation, are mentioned briefly.

Postoperative changes in the constituents of the blood and in the action of the heart are noted. The various postoperative complications and their relative incidences are listed and the over-all operative results in a series of forty-one cases are presented.

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A CASE OF TETRALOGY OF FALLOT WITH A PATENT FORAMEN OVALE (PENTALOGY) SHOWING A MARKED LEFT VENTRICULAR HYPERTROPHY AND LEFT AXIS DEVIATION

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BECAUSE the electrocardiographic demonstration of left axis deviation in patients with the cyanotic type of congenital heart disease has hitherto been considered diagnostic of tricuspid atresia,[1-3] we believe it significant to record a case of tetralogy of Fallot with a patent foramen ovale which presents a similar electrocardiographic picture.

CASE REPORT

A white girl, aged 9 years, was admitted to the University of Illinois Research Hospital with the following history: blueness of lips and fingernails since birth, puffiness of the face, hands, and feet during the previous week, and a dry, nonproductive cough for the previous month. She had been under constant medical care since birth. Eight days before admission to the hospital she awoke with edema of the face and two days later her hands, ankles, and feet also became swollen. Dyspnea on slight exertion, palpitation of the heart, and occasional dizzy spells with blurring of vision had been present since infancy. The family history was noncontributory. Her past history disclosed that she had chicken pox at the age of 8 years.

Physical examination revealed a dyspneic, cyanotic girl of 9 years, sitting in bed. Her temperature was 99.8° F., the pulse rate was 80, and the respiratory rate was 45 per minute. Her weight was 52 pounds; her blood pressure was 116/90. The skin was dry, scaly, and cyanotic. Marked edema of the feet, ankles, and sacrum was noted. There was no edema above the waistline. The mucous membranes, tympanic membranes, and finger and toenail beds were markedly cyanotic. There was marked clubbing of the fingers and toes. The lungs were clear on auscultation and percussion.

Cardiac enlargement was noted on percussion. The apex beat was in the sixth interspace in the anterior axillary line. There was a loud systolic murmur over the pulmonic area and at the apex. The abdomen was distended and the liver was palpable four fingerbreadths below the costal margin. The spleen and kidneys were not palpable. The following additional blood pressures were recorded: right arm 116/90, left arm 120/94, right leg 136/120, left leg 140/120. Ophthalmoscopic examination revealed hyperemic discs and slight retinal edema. The retinal veins were fuller and darker than normal.

The laboratory findings were as follows: the urine contained 2 to 3 plus albumin. Hemoglobin was 20.3 Gm. per 100 c.c., red blood count 9,220,000, white blood count 8,950.

The posteroanterior view of the chest (Fig. 1) showed a markedly enlarged transverse diameter of the heart, with the left border extending to the anterior

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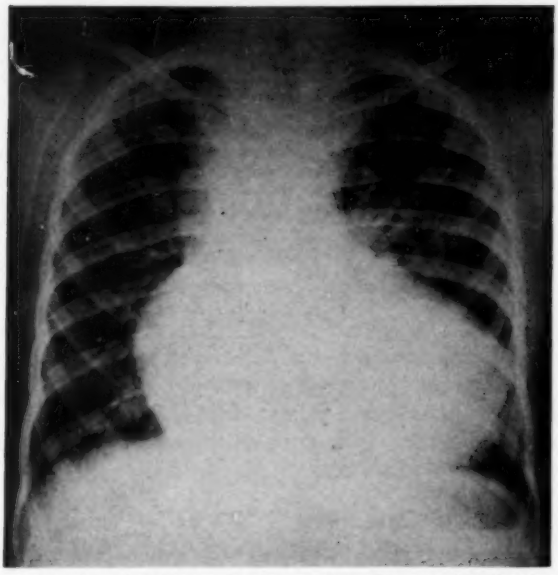

Fig. 1.—Posteroanterior view of the heart showing a mild enlargement at the transverse diameter with a concavity in the region of the pulmonary artery.

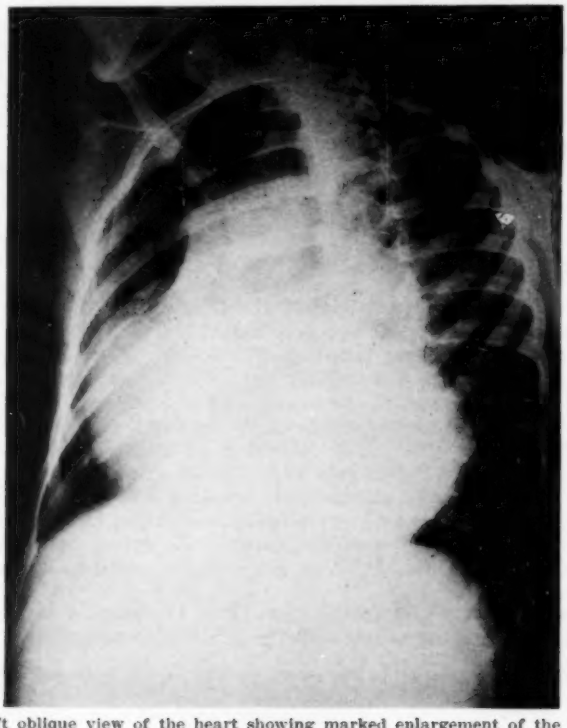

Fig. 2.—The left oblique view of the heart showing marked enlargement of the inflow tract of the left ventricle.

axillary line. There was a prominent concavity in the region of the pulmonary conus, and the pulmonary markings were somewhat more marked than normal.

The left oblique view (Fig. 2) showed a marked enlargement of the inflow tract of the left ventricle, with the latter not clearing the spinal column even on extreme rotation of the patient. The right auricle was also enlarged. Since the interventricular groove could not be visualized, it was difficult to determine the size of the inflow tract of the right ventricle.

The right oblique view (Fig. 3) showed a marked concavity in the region of the pulmonary conus.

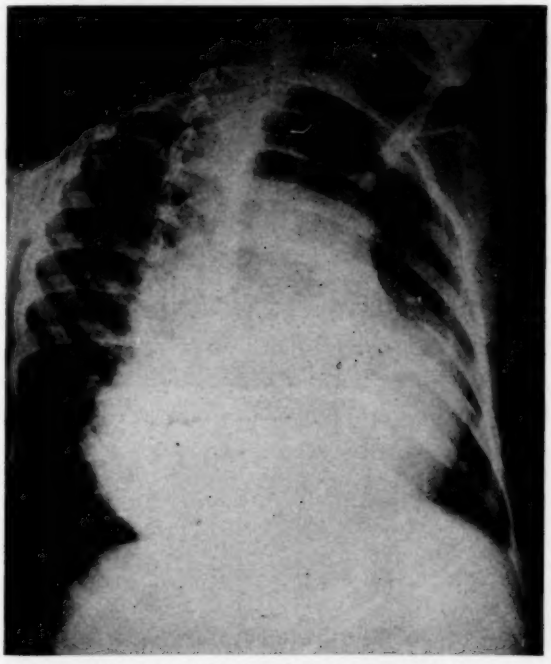

Fig. 3.—The right oblique view of the heart showing a concavity in the region of the pulmonary artery.

The electrocardiograms showed sinus rhythm, left axis strain, and first degree heart block. The QRS was upright in Lead I and deeply inverted in Leads II, III and CF_4. The P-R interval was 0.26 second; the QRS 0.07 second. P_1 and P_2 were tall, broad, and peaked (Fig. 4).

Attempts were made to reduce the edema by means of Mercupurin. Fifteen days after admission, immediately after a meal, she complained of pain in her abdomen and before a physician could reach her bedside she expired. An autopsy was performed twenty hours after death with the following findings:

There was generalized marked postmortem lividity but no peripheral edema. There was clubbing of the fingers and toes. The peritoneal sac contained 35 c.c. of clear, straw-colored fluid. There were no adhesions. The heart weighed 330 grams (normal for this age, 115 grams). It was markedly enlarged and associated with some epicardial thickening with a fair amount of

fat. The right auricle was huge, measuring 6 by 7 cm. in external dimensions. When opened, it presented a large, patent foramen ovale measuring 1.5 cm. in diameter, mild parietal hypertrophy particularly close to the base of the auricle, and distention of the auricular appendage with pronounced thinning of the auricular wall between the pectinate muscles. The tricuspid valve measured 6.5 cm. in circumference and presented a number of friable small,

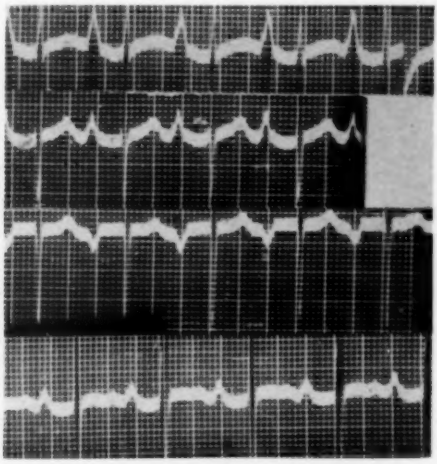

Fig. 4.—Electrocardiogram showing sinus rhythm, left axis strain, and first degree heart block.

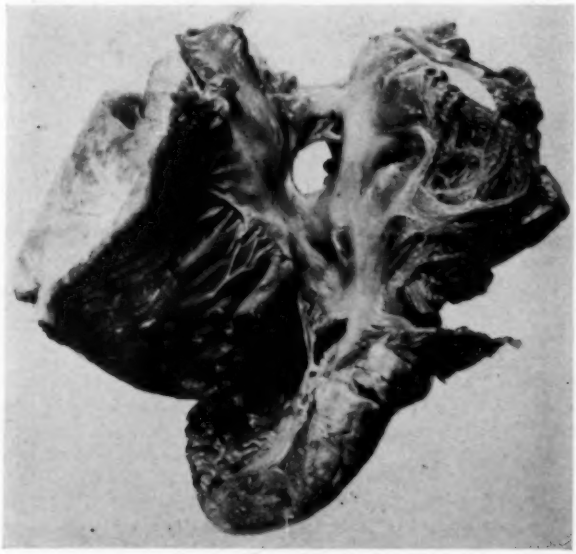

Fig. 5.—Right view of heart exposing greatly enlarged right auricle with a widely patent foramen ovale.

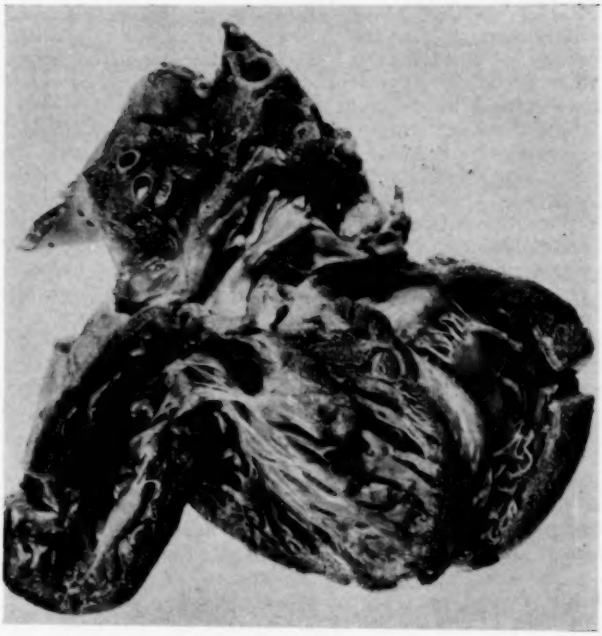

Fig. 6.—Photograph showing enlarged, hypertrophic right ventricle with a stenosis of pulmonary valve and an interventricular septal defect. Contrast thickness of right ventricle with that of left.

Fig. 7.—View of left side of the heart with a greatly dilated ventricular cavity with hypertrophy of its musculature exceeding that of the right ventricle.

pale vegetations near its free border, the largest not exceeding 0.4 cm. in greatest diameter. The right ventricle was dilated and its columnae carneae and walls were markedly hypertrophied. The thickness of the walls of the right ventricle varied in different places from 0.3 to 1.0 cm. There was stenosis of the pulmonary valve with, however, a normal conus. This valve measured 1.2 cm. in circumference and was bicuspid and fused. There was an interventricular septal defect immediately below the stenosed valve, with smooth margins which measured 1.8 by 0.9 cm. The aortic valve was well to the right of the interventricular septum, somewhat to the right and posterior to the stenosed pulmonary valve. It measured approximately 4 cm. in circumference, and presented three cusps with some submarginal vegetations similar to those on the tricuspid valve. The left auricle was in all respects somewhat smaller than the right and presented very slight hypertrophy of its musculature near its base. The mitral valve measured 5 cm. in circumference and was entirely normal except for a row of small, recent, friable vegetations near its free margin. The left ventricle was enlarged and its walls hypertrophied. Papillary muscles and columnae carneae were not particularly hypertrophied, however. The thickness of the wall of the left ventricle varied from 0.3 cm. at the apex to 0.8 to 1.5 cm. elsewhere. The pulmonary artery was thin-walled and measured approximately 2.5 cm. in circumference. Right and left major trunks were normally distributed. The aorta gave off four trunks, viz. the right subclavian, right common carotid, left common carotid, and left subclavian arteries. The ascending arch of the aorta measured 4.5 cm. in circumference and its wall appeared to be somewhat hypertrophied but with excellent elasticity and no trace of atheroma. The same held true to some extent for the rest of the aorta. The coronary arteries arose normally from the aorta, pursued normal courses, and, on dissection, presented no pathologic changes. The ductus arteriosus was essentially a cordlike structure without a definitely patent lumen. The bronchial arteries were not dissected, nor were they injected to demonstrate their size.

Lungs.—Each weighed 120 grams (normal for this age 174 and 152 grams, respectively). They were a little smaller than normal. There was in both a relatively mild passive congestion and some edema.

Gastrointestinal Tract.—The stomach was markedly distended with air. The intestinal tract otherwise was profoundly congested.

The spleen weighed 100 grams (normal 73). The liver weighed 935 grams (normal 756). The combined weight of the kidneys was 170 grams (normal 165). All these organs showed passive congestion, which was particularly marked in the liver and pancreas. The brain was not examined. The heart's blood culture yielded no growth.

The only findings of interest microscopically were in the heart. The vegetations were of bland, nonbacterial type and were undergoing organization. These same sections of valves revealed considerable fibrosis, principally the result of older organization of thrombi associated in all with little vascularity but in one section with an area of calcification. In addition to hypertrophy of myocardial muscle fibers there were areas of fibrosis, both perivascular and in that instance somewhat concentrically arranged, as well as irregular in outline and extent elsewhere in the myocardium. These latter in most instances probably represented healed areas of myocardial necrosis. There were rare, more recent necroses with cellular proliferation. Small, scattered foci of interstitial infiltration with polymorphonuclear and mononuclear cells were occasionally noted embedded in an edematous stroma.

Anatomical Diagnosis.—Diagnosis was tetralogy of Fallot with widely patent foramen ovale (pentalogy); nonbacterial verrucous endocarditis; focal

myocardial necroses (recent and old); interstitital myocarditis; passive congestion of viscera; ascites, mild; hydropericardium, mild.

COMMENT

Because of the unusual nature of this case, we believe it desirable to recapitulate our considerations prior to the death of the patient.

The history of cyanosis from birth, the marked polycythemia, and the clubbing of the fingers and toes definitely categorized this case as one of the cyanotic group of congenital malformations of the heart. The apparent enlargement of the left ventricle as demonstrated by fluoroscopic and x-ray examinations of the heart and confirmed by the electrocardiogram appeared to exclude the tetralogy of Fallot or a truncus arteriosus communis in which right ventricular enlargement is always present. A complete transposition of the great vessels could easily be excluded because children usually do not survive as long as our patient did with this malformation, and also because of the left axis deviation. In complete transposition of the vessels, the pulmonary markings should be prominent and one expects a definite narrowing of the base of the heart which widens in the left oblique view. None of these findings were observed. An isolated pulmonary stenosis was excluded because of the history of cyanosis from birth, and the left axis deviation. The vegetations noted on the valves were of the terminal, bland, nonbacterial, endocarditis type and of such a character that certainly with reference to the aortic valve there is no reason to suppose that they could have produced any insufficiency. The blood pressure readings also speak against this supposition. The myocardial necroses involved both ventricles. We, therefore, believed that the most probable diagnosis was a tricuspid atresia with an interauricular septal defect. We thought that the blood flowed from the right auricle into the left auricle through the interauricular septal defect, thence into the left ventricle and aorta and either into the pulmonary artery through the patent ductus, or into the right ventricle through an interventricular septal defect. Because the right ventricle in these cases is hypoplastic, the pulmonary artery would have to be stenosed, since a normal pulmonary artery cannot arise from a malfunctioning right ventricle. We explained the systolic murmur on the basis of either the pulmonary stenosis or interauricular septal defect.

The systolic murmur over the apex was considered to be due to either a relative mitral regurgitation resulting from an enlarged mitral ring, or as a murmur transmitted from the base. The apparent enlargement of the right side of the heart we believed to be caused by a markedly enlarged right auricle, and the tall, peaked P-waves appeared to substantiate this.

We were very surprised, therefore, when we learned from the autopsy that this was a case of tetralogy of Fallot with a patent foramen ovale. A search of the literature failed to disclose any case of tetralogy of Fallot with similar findings substantiated by autopsy. Brown, in his book on congenital heart disease, stated, "the finding of normal or left axis deviation in a cyanotic case should exclude a diagnosis of the tetralogy."[1] Maude E.

Abbott, in her *Atlas of Congenital Cardiac Disease,*[2] stated, "the roentgenogram in tricuspid atresia shows a left-sided enlargement that is characteristic and of diagnostic value, as is the left axis deviation seen in the electrocardiogram in these 'right-sided lesions' of the cyanotic group." Helen B. Taussig, in her book on *Congenital Malformations of the Heart,*[3] states, "the electrocardiogram always shows a marked right axis deviation in Tetralogy of Fallot." Only Calo,[4] in 1937, reported a case of what appeared clinically to be a tetralogy of Fallot with left axis deviation and a bundle branch block, but no autopsy was performed in this case.

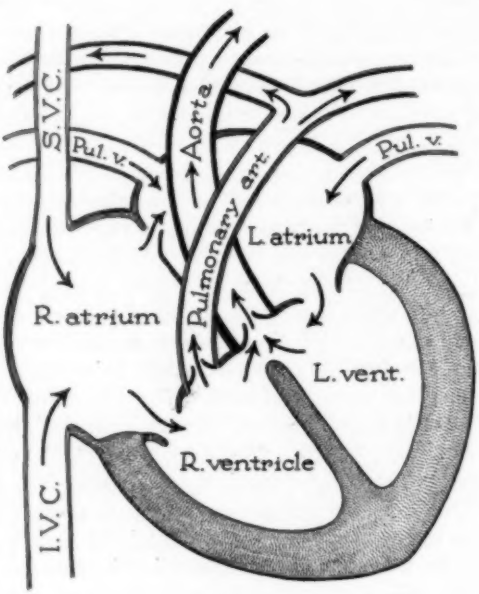

Fig. 8.

In attempting to explain the left axis deviation and the marked hypertrophy of the left ventricle, we must conclude that the presence of the associated patency of the foramen ovale resulted in a shunt from the right to left side of the heart in this case (Fig. 8). The hemodynamics are probably very similar to that of a tricuspid atresia or stenosis. The pressure in the right auricle must have been higher than that in the left auricle and part of the blood probably flowed from the right into the left auricle, while the remainder flowed into the right ventricle. The additional blood flowing into the left auricle and thence into the left ventricle probably resulted in a gradual hypertrophy and dilatation of both of these chambers. The right ventricle in this case was also hypertrophied because of the stenosis of the pulmonary valve and the dextroposition of the aorta. We believe, therefore,

that a patent foramen ovale in association with a tetralogy of Fallot may in some instances result in hypertrophy of the left ventricle sufficient to produce a left axis deviation in the electrocardiogram.*

SUMMARY

The clinical and pathologic findings in a case of tetralogy of Fallot associated with patent foramen ovale are presented. It is believed that this is the first reported case of a tetralogy of Fallot with a hypertrophy of the left ventricle and a left axis deviation substantiated by autopsy.

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*Recently we have observed autopsies of two infants with Tetralogy of Fallot and patent foramen ovale whose electrocardiograms showed marked right heart strain. This suggests that the mere presence of the patent foramen ovale is not the determining factor in the production of a left heart strain. The blood must be shunted from the right auricle into the left one for a considerable length of time (probably a number of years) before the left ventricle hypertrophies and dilates.

THE USE OF CAROB FLOUR IN THE TREATMENT OF DIARRHEA IN INFANTS AND CHILDREN

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EARLY in 1948, following an unsatisfactory experience in the treatment of a series of infants with acute diarrheal disturbances, it was decided to follow the suggestion of a European pediatrician to test an antidiarrheic substance which has been used by European physicians in recent years but to the best of our knowledge has not been used in this country. The product, which is known commercially in Europe as "Arobon," is derived from the bean of the carob tree and contains added starch. Except for the use of this product, the therapy of the acute diarrheal disturbances in the infants to be reported here was not materially different from that previously used. It consisted of the commonly employed regime of an initial period of "starvation" during which water and electrolytes were administered by oral and parenteral means,[16] followed by gradual increments in oral feeding.

Certain fruits and products prepared from them have been used for some years[1-7] in the treatment of diarrhea. Fully ripe apples and bananas, in particular, have been recommended and are available in the dried state in a number of preparations.[8-12] During the Spanish Civil War and at the beginning of the World War II, Ramos[13] of Barcelona, Spain, faced with the increasing difficulty of procuring such dietetic products, sought other material for therapeutic use. He had noticed that during the war in Spain, the children of the poorer classes in Barcelona who ate the fruit of the carob tree had fewer diarrheal disturbances than did those of the wealthier classes. Based on this observation, he employed the dried pulp of the roasted carob mixed with starch for the treatment of diarrhea.

The carob[14, 15] is the fruit of the carob tree, a leguminous plant which is native to the shores of the Mediterranean. This fruit is a bean-shaped pod, approximately 12 to 20 cm. long and 2 cm. wide. The pod contains a sweet pulp, pleasant to the taste; it is rich in sugar (more than 40 per cent) and low in protein (about 4 per cent). When dried, it furnishes a flour which remains in a fine suspension in water.

Carob pulp contains less cellulose and far less pectin than the apple or banana, but on the other hand it is very rich in lignin, a substance of a higher molecular weight than cellulose or pectin. The properties of lignin compare with those of pectin but differ considerably from those of cellulose. It is believed that the carob bean owes its unusual mechanical and disintoxicating properties to lignin.[14, 15] Carob flour, distended with water, gives greater mass to the

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Material for this study has been kindly supplied by The Nestlé Co., Inc.

stools. The stools become dark brown in color, and, since they contain less water, dry increasingly rapidly as intestinal function returns to normal and their number diminishes.

The carob flour, as prepared under the name of "Arobon," contains 12 per cent added starch. Its taste is somewhat similar to that of cocoa, being pleasant only if the flour is sweetened with saccharin. The flour has the following composition:

Fat (ether extract)	0.5 per cent
Protein (N × 5.7)	3.5 per cent
Soluble carbohydrate (sucrose and reducing sugars)	49.0 per cent
Other carbohydrate (hemicellulose and pectin)	22.0 per cent
Starch	13.0 per cent
Crude fiber	6.0 per cent
Minerals (ash)	2.5 per cent
Moisture	3.5 per cent
Calories	250 per 100 Gm.
1 oz. by dry weight equals	75 calories
1 tablespoonful equals	19 calories

METHOD OF STUDY

The plan of treatment included an initial period of "starvation," during which food other than water and electrolytes was withheld. In nineteen of the thirty infants in the study group, fluids were administered parenterally. In general, the plan recommended by Butler[16] was followed. Plasma and blood transfusions were given to some infants, as were penicillin, streptomycin, and/or one of the sulfonamides. At the end of the "starvation period," approximately twenty-four to thirty-six hours, the carob flour formula was started.

For infants less than 6 months of age, the formula contained 2 teaspoonfuls of carob flour for each 3½ oz. of water (5 per cent by weight). An average daily fluid intake of 2½ to 3 ounces per pound of body weight was maintained. For infants more than 6 months of age, a more concentrated carob formula was used, the ratio being 4 teaspoonfuls of carob flour to each 3½ oz. of water (10 per cent by weight). When the stools were well formed and dark brown in color, acidified powdered milk was added to the diet in the proportion of 2 teaspoonfuls to each 3½ oz. of the carob flour mixture. If the milk was tolerated and diarrhea did not recur, the quantity of milk in the formula was increased and that of the carob flour decreased.

RESULTS

The data are summarized in Table I. Thirty infants, varying in age from 2 days to 15 months, with acute diarrheal disturbances were given the carob flour formula as part of their therapy. The formula was well tolerated even by the smallest infants. The effectiveness of the carob flour therapy was meas-

TABLE

NAME	AGE	DIAGNOSIS	DAYS OF ILLNESS BEFORE ADMISSION OR START OF "AROBON"	NUMBER OF STOOLS ON DAY BEFORE ADMISSION	PRESENCE OF ACIDOSIS*
J. T.	4 mo.	Diarrhea, dehydration, congenital hypothyroidism	3	5	No
S. S.	4 mo.	Diarrhea	2	6	No
A. T.	4 mo.	Diarrhea, feeding problem, malnutrition, pneumonia	3	6	No
C. W.	5 mo.	Diarrhea, vomiting, dehydration	2	6	Yes
Baby C.	2 weeks	Allergy to milk	7	7	No
P. M.	3 mo.	Diarrhea	3	5	No
P. di S.	4 mo.	Diarrhea, dehydration	2	9	No
D. P.	5 mo.	Diarrhea, malnutrition	2	3	No
G. W.	2½ mo.	Diarrhea, dehydration, bronchopneumonia	1	4	Yes
C. R.	1 mo.	Diarrhea	2	4	No
J. L., Jr.	1 mo.	Diarrhea, dehydration, bronchopneumonia	1	12	Yes
Baby J.	1 week	Diarrhea, dehydration, pneumonia	1	4	No
M. F.	3 weeks	Diarrhea, dehydration	4	5	Yes
Baby W.	2 days	Diarrhea, cleft lip, cleft palate	1	10	No
R. J.	7 mo.	Diarrhea, dehydration, malnutrition, eczema	4	8	Yes
G. G.	5 weeks	Diarrhea	2	9	Yes
W. B.	4 mo.	Diarrhea, double aortic arch	2	4	No
F. B.	5 mo.	Diarrhea, dehydration, feeding problem	3	6	Yes
J. K.	5 mo.	Diarrhea, tracheobronchitis	2	10	Yes
J. H.	2½ mo.	Diarrhea, tracheobronchitis	16	5	Yes
J. D.	2 weeks	Diarrhea, dehydration	3	8	Yes
E. R.	1 week	Diarrhea, dehydration	2	3	Yes
V. H.	1 mo.	Diarrhea, dehydration	3	8	No
F. R.	7 mo.	Diarrhea, dehydration	2	10	No
R. S.	14 mo.	Diarrhea, dehydration	3	3	Yes
K. M.	14 mo.	Diarrhea, dehydration	1	7	Yes
M. M.	2 weeks	Diarrhea, dehydration	5	12	Yes
Baby B.	1½ weeks	Diarrhea, dehydration	2	7	No
J. McK.	15 mo.	Diarrhea, dehydration, malnutrition, pneumonia	3	10	Yes
V. P.	2 weeks	Diarrhea, dehydration	3	11	Yes

*Criteria for diagnosis of acidosis: symptomatology, blood carbon-dioxide combining power, and urinalyses were evaluated.

†"Cure" means the achieving of formed stools and their remaining so after the addition of milk to the diet.

ured by the antidiarrheic action. Shortly after its administration, changes in the color, appearance, and consistency of the stools were observed. They became dark brown in color, homogeneous, and firm. In eleven infants the stools became formed ("carob stools") after one day of carob flour therapy (immediate effect); in twelve infants, after two days (rapid effect); in six infants, after three days (slow effect). In only one infant was there no antidiarrheic effect.

The effect on the weight curve was in more or less direct relationship to the condition of the stools. The average gain in weight was 6½ ounces.

Some of the infants regurgitated two or three sips of the carob flour formula after each feeding. Vomiting was never a serious factor, however, nor was it a sign of intolerance.

I

NUMBER OF DAYS AFTER ADMISSION TO ACHIEVE "CURE"†	WEIGHT ON ADMISSION (LB.—OZ.)	WEIGHT ON DISCHARGE (LB.—OZ.)	NUMBER OF DAYS IN HOSPITAL	GAIN OR LOSS IN WEIGHT (LB.—OZ.)	RAPIDITY OF EFFECT FROM CAROB FLOUR	FLUID REPLACEMENT THERAPY
4	6 13	7 2	5	5	Slow	Clysis
3	11 4	11 7	13	3	Rapid	
3	11 10	11 11	11	1	Rapid	
2	18 10	18 13	6	3	Immediate	Clysis
4	8 4	9 0	30	12	Slow	
2	11 0	11 4	8	4	Immediate	
4	10 6	10 10	15	4	Slow	Clysis
2	8 13	9 4	8	7	Immediate	
4	10 5	10 11	8	6	Slow	Intravenous
4	6 12	7 15	12	1 3	Rapid	
4	8 3	8 8	17	5	Rapid	Intravenous
4	6 6	6 5	11	−1	Slow	Clysis
2	6 12	7 2	8	6	Immediate	Intravenous
3	7 7	7 0	8	−7	Rapid	Clysis
4	10 7	11 15	20	1 8	Rapid	Intravenous
2	7 9	8 0	9	7	Immediate	
2	15 4	14 14	5	−6	Immediate	
2	10 1	10 15	10	15	Immediate	Clysis
4	10 9	10 5	12	−4	Immediate	
3	12 0	11 4	20	−10	Rapid	
Failure	–	–	–		Failure	Intravenous
4	5 5	5 14	13	9	Slow	Clysis
3	5 4	5 4	8	0	Rapid	Clysis
3	13 3	13 0	9	−3	Rapid	Intravenous
2	18 10	18 10	8	0	Immediate	Intravenous
2	20 9	21 8	6	15	Immediate	Intravenous
4	5 10	6 1	11	7	Rapid	Intravenous
2	6 11	6 11	9	0	Immediate	Clysis
3	17 8	21 8	6	4 0	Rapid	Intravenous
3	7 7	8 3	16	12	Rapid	

CONCLUSIONS

Initial and limited experience with carob flour ("Arobon") in the treatment of acute diarrheal disturbances in infants has been encouraging. Disappearance of diarrheal stools appears to be hastened, thus permitting early re-alimentation and hydration by the oral route. Further clinical trial and comparison with other hygroscopic agents is indicated.

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FEBRILE CONVULSIONS IN CHILDHOOD: THEIR RELATIONSHIP TO ADULT EPILEPSY

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THE significance of febrile convulsions is a matter of dispute, with opinion divided as to their significance and relationship to adult epilepsy. Husler[1] states that febrile convulsions bear no relationship to epilepsy. Faerber[2] believes that in some patients febrile convulsions are indistinguishable from epilepsy.

Thom[3] and Patrick and Levy[4] differ as to the exact amount by which an individual's chances of developing epilepsy are increased by infantile convulsions. They agree, however, that "it seems evident that infantile convulsions do tend to increase materially the risk of epilepsy and mental deficiency in later life."[3] Both state that febrile convulsions are of less serious import than convulsions assigned to trauma or for which no cause can be found. Livingston, Bridge, and Kadji[5] report seventy-six cases in patients whose first convulsion was attributed to fever and who have been followed fifteen years. Sixty of these patients developed recurrent convulsions without fever. In a previous study[6] we suggested that febrile convulsions appear to differ from epilepsy in degree rather than in kind. Since severity in epilepsy can be expressed only in terms of the number of spells (for any one type of spell) it is clear that, if our conception is correct, febrile convulsions represent an extremely mild form of the disease.

Whatever one's formulation as to the fundamental significance of febrile convulsions, it is possible for all observers to agree that the majority of children with febrile convulsions will have no further seizures during the rest of their life. Agreement can also be assured that a certain number of children with febrile convulsions will have adult epilepsy. Estimates as to the percentage of children who will be affected vary from 5 to 10 per cent. The percentage is probably of less practical importance than the determination of prognostic guides; it is of practical importance to have some clues as to which children may develop epilepsy and why, so that this outcome may be prevented if possible. Patrick and Levy[4] emphasize the serious prognostic import of severe or focal convulsions. The free periods reported by them are interesting: in 40 per cent the interval was ten years or longer. These results contradict the contention of Livingston and associates[5] that convulsions without fever do not occur at all if they have not started by the time the child is 5 or 6 years old, i.e., the first five years indicate the prognosis. In a previous study[6] we found age at onset, sex, and family history to be of prog-

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nostic importance, but agreed with Patrick and Levy[4] that the severity of the convulsion is by far the most important feature in the history. We have also found that the electroencephalogram has definite prognostic significance.[7]

Aside from the importance of febrile convulsions with respect to the development of epilepsy, febrile convulsions may cause brain pathology as evidenced by transient or permanent neurological deficit. Fever alone can cause brain pathology,[8] as can convulsions.[9] The combination of fever and convulsions is more damaging than either fever or convulsions alone.[10] This susceptibility to brain pathology as a result of fever and/or convulsions characterizes infants almost exclusively and is not apparently related to the special susceptibility of infants to convulsions.[10]

We have extended our previously reported series of epilepties whose first convulsion occurred with fever. The early histories of these patients have been investigated and compared with the histories of children with febrile convulsions (most presumably benign) in an attempt to determine which clinical features suggest that further convulsions will develop.

METHOD AND MATERIALS

The subjects consist of children and adults referred to the Electroencephalography Laboratory because of recurrent seizures. If the first convulsion was attributable to fever and if the history was sufficiently detailed and accurate, the case was included in this study. Most cases were referred with such brief histories that we could not include them. For the most part, those included are patients admitted to the in-patient service whose histories are available, and patients referred to seizure clinic. Twelve of the seventy-seven patients referred for electroencephalography because of febrile convulsions later developed recurrent seizures without fever.

The histories were reviewed in order to obtain the following information: sex; age at onset; number of febrile convulsive episodes; severity of convulsions (for the purpose of this study, a convulsion was classified as severe if it lasted an hour or more, or if it started in or involved only one limb or one side of the body); family history of convulsions; height, duration and cause of fever; mental retardation (children were classified as retarded if the I.Q. was below 80 or if there was marked clinical evidence of developmental retardation); and birth history (classified as abnormal were breech deliveries, placenta previa with severe bleeding, high or middle forceps, cesarean delivery, twin birth, prematurity if the birth weight was less than 5 pounds, and hemorrhagic disease of the newborn infant).

The histories of these epileptic patients were compared with histories, similarly obtained, of 240 children with febrile convulsions, most of them presumably benign.

The electroencephalograms were obtained with four, six, and eight-channel Grass ink-writing electroencephalographs. Electrodes were placed on the frontal, central, parieto-occipital and temporal areas on both sides and were recorded with reference to interconnected, grounded ear leads and, in many instances, scalp-to-scalp and scalp-to-alternate-ear recordings were ob-

tained as well. Controls consisted of 373 normal unscreened children whose electroencephalograms were obtained in the Pediatric Clinic of the Grace-New Haven Community Hospital with the collaboration of Dr. Donal L. Dunphy, and at the Boston Children's Hospital. The latter records were made available to us through the courtesy of Dr. F. A. Gibbs and Mrs. E. L. Gibbs. In addition, we relied on the descriptions of normal electroencephalograms in the Gibbs' *Atlas of Electroencephalography*[11] and in the monograph by C. E. Henry.[12]

Electroencephalograms were classified according to the classificatory system of Gibbs, Gibbs, and Lennox.[13] Records showing extreme slowing, with a predominance of high-voltage, rolling, one to three per second waves, were classified separately. Originally records in which slow waves appeared predominantly or exclusively in the occipital leads were classified separately, but we are now forced to the conclusion that these electroencephalograms are normal, and we have included them in the normal group.

RESULTS

The group of seventy-seven epileptic patients whose first convulsion was attributable to fever in every case ranged in age from less than one year to 45 years. One-half the patients were 5 years old or younger. The time interval from the last febrile convulsion to the first nonfebrile convulsion varied from a few months to twenty-five years; in the majority it was within the first year. All types of convulsions occurred. More than one-half were grand mal, and one-third of the patients had symptoms indicating focal onset of the convulsions. Seven were classified as petit mal and six as psychomotor.

The electroencephalograms of the patients in this group were varied. Approximately one-third were normal, one-third paroxysmal, one-sixth focal, and the rest nonspecifically abnormal, i.e., fast or slow.

Prognostic features which appeared to be of importance concerned age at onset, sex, number of febrile convulsive episodes, and family history (Table I). By far the most important item in the history, however, was the severity of the convulsion.

As compared with children with presumably benign febrile convulsions, patients whose febrile convulsions presaged epilepsy had an earlier age at onset (before one year in one-third), with more than three convulsions in a higher percentage of cases, and a higher percentage of epilepsy (as opposed to infantile or isolated convulsions) in the family history. Whereas boys outnumber girls in the febrile convulsive group by two to one, girls outnumber boys slightly in the epileptic group. Presumably this is due to the inclusion in this group of patients with petit mal epilepsy, which is more common in girls. Whatever the reason, it is apparent that the risk of developing epilepsy is greater for girls than for boys.

By far the most important prognostic feature is the severity of the convulsion. A severe convulsion with fever occurred in 61 per cent of epileptic patients, whereas it occurred in 40 per cent of "benign" febrile convulsions.

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TABLE I. CLINICAL CHARACTERISTICS OF CHILDREN WITH FEBRILE CONVULSIONS AND OF CHILDREN WHOSE FIRST CONVULSIONS OCCURRED WITH FEVER BUT WHO LATER DEVELOPED RECURRENT SEIZURES WITHOUT FEVER

CLINICAL DATA	FEBRILE CONVULSIONS		EPILEPSY (FIRST CONVULSION FEBRILE)	
	NO. PATIENTS	%	NO. PATIENTS	%
Number	240	—	77	
Sex: male	149	62.1	36	46.8
female	91	37.9	41	53.2
Age at onset	236	—	75	—
1 year	54	22.9	25	33.4
1-2 years	149	63.2	40	53.4
3-4 years	23	9.7	8	10.7
5-7 years	10	4.2	2	2.5
No. febrile convulsive episodes	240	—	76	—
One or two	197	82.0	47	62.0
Three or more	43	18.0	29	38.0
Severity of febrile convulsions	176	—	53	—
Mild	106	60.2	20	37.6
Severe	70	39.8	33	62.3
Mental development	162	—	68	—
Normal	127	78.4	53	78.0
Abnormal	35	21.6	15	22.0
Birth History	187	—	66	—
Normal	136	72.8	49	74.3
Abnormal	51	27.2	17	25.8
Family history	199	—	66	—
None	109	54.8	41	62.1
Convulsions	90	45.2	25	37.9
(Epilepsy)	14	7.0	9	13.6
(Rare convulsions)	76	38.2	16	24.3
Both sides	11	5.5	4	6.2

Severe convulsions were more than twice as common under 3 years of age than at ages of 3 years and over.

There was no difference between the two groups with reference to cause of fever. The height of the fever tended to be somewhat lower in the epileptic group, since one-half had a convulsion with a recorded temperature of 102° or less. Duration of fever was not known in enough patients to allow any conclusions to be drawn. There was no difference in birth history between the two groups, but if one considers only children under 5 (in whom the birth history is most likely to be accurate) 38 per cent had an abnormal birth history in the epileptic group as opposed to 27 per cent in the "benign" group. This supports the observation that an abnormal birth, even though no clinical symptoms are observed at the time, tends to increase the hazard of epilepsy.

The electroencephalogram appears to have definite prognostic value. Even in an inadequate three-year follow-up period, it has been possible to show a correlation between the electroencephalogram (taken within a week of the febrile convulsive episode) and the development of nonfebrile convulsions. Of patients with a normal electroencephalogram, 5 per cent have developed

convulsions without fever. By contrast, 17 per cent of patients with a moderately slow electroencephalogram, 25 per cent of patients with a paroxsymal electroencephalogram, 33 per cent of patients with an extremely slow or focal electroencephalogram, and 50 per cent of patients with an abnormally fast electroencephalogram have developed convulsions without fever. The figures cannot be thought of as definitive, but it is evident that an electroencephalogram is as important as a careful history in judging prognosis. Mistakes will occur in both directions: some children in whom every sign points to the "benignity" of the febrile convulsions will develop epilepsy. Some who have all the cards stacked against them will escape. In general, however, the clinical history and the electroencephalogram afford an indication as to the chances that epilepsy will develop.

Case histories which illustrate the predictability and unpredictability of the outcome follow:

CASE 1.—E. K., a 31-year-old unmarried white woman, was seen because of grand mal and psychomotor seizures which started at the age of 17 years. Past history revealed that at the age of 4 months she had a convulsion lasting three hours, attributed to fever, and caused by a respiratory infection. She was then entirely well until the age of 5 years, when she developed "feelings" which occurred several times a day in the summertime only and lasted until she was 10 years of age. She is completely unable to describe these feelings, but can only say that things looked strange to her. The "feelings" lasted a few minutes at a time and were not accompanied by loss of consciousness. She was again symptom-free until the age of 17 years, when monthly grand mal and more frequent psychomotor seizures commenced. The psychomotor seizures occur as often as fifteen a day and the longest free interval has been eight months; during the seizures the patient first has her aura of an indescribable "feeling." She then loses consciousness, stiffens, turns blue about the lips, and swallows repeatedly.

Birth was normal. There was no head injury or severe illness other than the one at 4 months of age. Family history is negative for convulsions.

The electroencephalogram shows paroxsymal slow waves.

Comment.—A prolonged febrile convulsion at the susceptible age of 4 months apparently caused the pathology responsible for the patient's later focal, psychomotor, and generalized motor convulsions. In this case there was no family history of convulsions, so the attacks are assumed to be "acquired." The long free period between the patient's initial insult and first focal seizure symptoms is interesting, as is the long remission between these focal symptoms and the development of major attacks. The potential seriousness of a febrile convulsion in a child under one year of age is evident from this case.

CASE 2.—D. G., a girl aged 14 years, was seen because of psychomotor seizures which started at the age of 7 years. She was born by breech delivery. At the age of 2 years, with a temperature to 104.5° F. due to pneumonia, she had repeated convulsions for seven hours. She recovered uneventfully and had no more seizure symptoms until the age of 7 years, when she developed psychomotor seizures. These seizures last as long as fifteen minutes, during which she is out of contact. She usually remains motionless, often leaning her head on her hand, but may continue activities inaccurately or do things she would

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not ordinarily do, such as stepping out of a moving car. All of these spells are preceded by a peculiar feeling which the patient finds it impossible to describe. Sometimes there is only partial loss of consciousness when she "hears voices far away as if in a dream. . . . The words don't make sense."

Family history is negative for convulsions.

Electroencephalogram reveals two to three per second waves in the contralateral temporal lead on recording to alternate ears. On medication the electroencephalogram is normal.

Comment.—In view of the negative family history, the patient's seizures are assumed to be primarily acquired. Although the breech delivery may have contributed to the brain pathology, prime responsibility is assigned to the seven-hour febrile convulsion which the patient experienced at the age of 2 years. Clinical and electroencephalographic findings point to the temporal lobe as the site of origin of the epileptic disturbance and presumably as the site of the brain pathology.

CASE 3.—A. B., a girl, was seen at the age of 12 years because of petit mal spells which started at the age of 10 years. Past history revealed that the patient had five brief convulsions with fever, the first at the age of 8 months and the last at 5 years. The family history was positive in that the father had convulsions until the age of 12 years, and a brother had one brief convulsion at the age of 3 years at the onset of fever due to pneumonia. Past history and birth history were normal. Electroencephalogram was diagnostic of petit mal epilepsy.

Comment.—In this patient the positive family history suggests that the epilepsy is primarily "genetic" and that the febrile convulsions were the first evidence of epilepsy. The only historical item suggestive that secondary factors may have played some role in the development of epilepsy is the fact that the first convulsion occurred when the patient was not yet one year old, a time when brain pathology is most readily produced.

CASE 4.—G. M., a female child, was referred for electroencephalography at the age of 2 years, 3 months. She was born after a long labor but there was no apparent injury and development was normal. Family history was positive in that the mother had many convulsions in a two-week period in infancy, but recovered uneventfully and had no subsequent convulsions.

At the age of 10 months the patient had a convulsion lasting a few minutes with a temperature to 103° F. At 11 months she had repeated right-sided convulsions for twenty-four hours. Temperature reached 107° F. during the first day, and some elevation lasted four days. When she was first seen two months after the acute episode, she had a right spastic hemiparesis, a right homonomous hemianopsia, and a left-sided electroencephalographic focus. Eighteen months later her physical and electroencephalographic findings had not changed, but she had had no further convulsions.

Comment.—All features in this case, the difficult birth, occurrence of prolonged convulsions with high fever at less than one year of age, electroencephalographic and physical evidence of brain damage, and positive family history, suggest the likelihood that epilepsy will develop, yet this has not as yet happened. Admittedly the eighteen-month follow-up period is far too short.

CASE 5.—R. G., a male child aged 2 years, 10 months, was admitted to the New Haven Hospital because of one ten-minute grand mal convulsion. This occurred with a temperature of 104° F. caused by pneumonia. Temperature subsided in three days. A waking and sleeping electroencephalogram was obtained six days after the acute episode and was normal. Past history was unrevealing except that the patient had measles at the age of 2 years. Birth and development were normal. Family history was negative for convulsions.

The patient did not return to the hospital, but a nurse made a home visit three years after the initial episode. At this time the patient was six and had been entirely well until six months previously when recurrent convulsions without fever developed.

Comment.—Age at onset, brief convulsion, negative family, birth, and developmental history, and normal electroencephalogram all suggested that the patient's one febrile convulsion was benign. Yet recurrent convulsions without fever started at the age of 6 years.

DISCUSSION

Interest attaches to febrile convulsions because of their frequency, their unexplained clinical characteristics, their short-term sequelae, and their relationship to adult epilepsy.

Convulsions in children under 5 years of age are surprisingly frequent; they occur in 5 per cent[3] to 7 per cent[4] of the normal population, and are attributable to fever in one-half of the cases.

The clinical features of febrile convulsions are well known; in two-thirds of the cases they occur in boys between the ages of one and 3 years with a rapid elevation to a temperature of 103° F. or more. The fever is usually attributable to respiratory infection and is usually of short (one-two days') duration.[7] Although Patrick and Levy[4] state that all "benign" febrile convulsions are mild, severe convulsions occurred in 40 per cent of our presumably "benign" cases.[7] The family history is positive for convulsions, usually infantile, in 45 per cent of our cases, and in 3 per cent of children who do not have convulsions with fever.[4] These facts are well known, yet no explanation for the peculiar susceptibility to febrile convulsions is known to us.

Although fever is most often complicated by convulsions at the ages of one and 2 years, it is most likely to produce brain pathology in young infants under the age of one year.[10] This is another peculiar age susceptibility for which there is no apparent explanation. When convulsions complicate the fever, the hazard of brain pathology is greatly increased, and this is especially so if the convulsions are severe or the fever prolonged.[10] Severe convulsions occurred twice as often under 3 years as over that age in this series. It is thus apparent that children under 3 years with febrile convulsions run a greater risk of brain pathology than do children with fever or febrile convulsions over 3 years old. Sometimes the only evidence for brain pathology is an extremely slow electroencephalogram in the first week after the acute episode, sometimes prolonged coma or drowsiness, sometimes transient or permanent neurological

findings, or mental retardation. Sometimes the only evidence of brain trauma inflicted by the febrile convulsion is the development, after months or years, of seizures often of focal onset or nature. Cases 1 and 2 are examples of this.

For brain pathology incurred as the result of the combined effect of fever and convulsions is one of the prime factors predisposing to the development of recurrent seizures or epilepsy. This accounts for the clinical finding that the occurrence of febrile convulsions before the age of one year, and the occurrence of severe convulsions both carry relatively serious import for the development of recurrent nonfebrile convulsions. This also accounts for the relatively serious import of extremely slow and focal electroencephalographic abnormalities within a week of the convulsion. Brain damage attributable to birth injury also increases the likelihood that epilepsy will develop, especially if it is evidenced by an abnormally fast electroencephalogram.[7]

In other instances the epilepsy appears to be genetically determined, and in these cases, as in Case 3, one agrees with Faerber[2] that the febrile convulsions were the first evidence of epilepsy.

Most often there are evidences that both genetic and acquired, often multiple acquired factors are jointly responsible for the development of epilepsy. "It is the purpose of this article . . . to point out that *in a single individual* (with seizures) the etiological factors are usually multiple."[14]

The prevention of brain pathology and the prevention of epilepsy are aspects of the same problem, and require the prevention of prolonged fever in infants under one year of age and of severe febrile convulsions in infants under 3 years of age. If a child has had a febrile convulsion, reliance cannot be placed on aspirin and phenobarbital in the event of a fever to avoid further convulsions, since the convulsion is often the first evidence of the fever. It is more effective to give regular anticonvulsant medication to children under 3 years of age after the first febrile convulsion, and to make a vigorous effort to shorten a convulsion, when it occurs, as well as its precipitating fever. The prevention of brain pathology also depends on the prevention of anoxemia[8] and of dehydration[10] insofar as is possible.

In conclusion, with reference to the significance of febrile convulsions, subsequent experience has not caused us to change the opinion expressed three years ago. "We do not wish to deny what is well known—that the great majority of children with febrile convulsions will have no further seizures during the rest of their life. We do wish to emphasize the many interconnections between 'epilepsy' and febrile convulsions. We have been struck by the prominent hereditary factor demonstrated in febrile convulsions, and the relative frequency with which children with febrile convulsions develop recurrent seizures as compared with the 'normal' population. If one defines epilepsy as a disease characterized by recurrent seizures, one must certainly exclude from this category the majority of children with febrile convulsions. If one applies the broader and possibly more accurate definition of epilepsy as 'hereditarily determined convulsions,' then febrile convulsions would certainly be classed as 'epilepsy.' According to this conception, febrile convulsions differ from epilepsy as a disease only with respect to severity, but there

is no real difference in kind. This formulation appears to fit the facts better than the assumption that epilepsy and febrile convulsions are two distinct disease entities and have nothing to do with each other."[6] To the objection "but we can't call febrile convulsions epilepsy, for if we do, then some of our best people have epilepsy" we can only assent that some of our best people do, indeed, have epilepsy.

SUMMARY AND CONCLUSIONS

1. Clinical histories of patients with febrile convulsions are compared with the histories of patients with epilepsy whose first convulsions were febrile.

2. Unfavorable prognostic features, suggesting the likelihood that recurrent seizures may develop, are: an early age at onset (under one year); prolonged or focal convulsions; an abnormal birth history; a history of many febrile convulsive episodes; a family history of epilepsy; an abnormal electroencephalogram; and female sex. Most often several of these factors in combination appear to be responsible for the development of epilepsy.

3. The prevention of epilepsy requires the prevention of prolonged fever in children under the age of one year and of prolonged or focal convulsions in children under the age of 3 years.

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EVALUATION OF THE COOMBS TEST IN CONGENITAL HEMOLYTIC DISEASE OF THE NEWBORN INFANT

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IN 1945 Coombs, Mourant, and Race[1] described a new method for the detection of Rh antibodies by the use of a serum prepared from rabbits immunized with human serum or its globulin fraction. This serum is used to demonstrate the presence of a form of Rh antibody which apparently is adsorbed on the surface of erythrocytes. When the test is positive, visible clumping of the affected red blood cells occurs, and this reaction has been referred to as the Coombs test or developing test.[2] The test is of considerable practical value in congenital hemolytic disease of the newborn infant, or erythroblastosis fetalis, in which condition it has been used to detect a type of maternal Rh antibody and to examine the erythrocytes of the newborn infant for adsorbed antibodies. The test is not specific for Rh antibodies as it is also positive in cases of acquired hemolytic anemia not due to Rh sensitization.[3] The purpose of this paper is to indicate the value of the Coombs (developing) test in the diagnosis and management of congenital hemolytic disease of the newborn infant.

Since 1948 several hundred Coombs tests have been performed in the laboratory of this hospital on the blood of newborn infants in order to rule out congenital hemolytic disease of the newborn infant. The usual indications for the performance of the test were (1) early onset of jaundice in a newborn infant, (2) infants born of Rh negative mothers in whom there may or may not have been a previous examination for Rh antibodies and (3) cases of congenital hemolytic disease and related conditions requiring differential diagnosis. Twenty cases have been selected from this latter group as illustrative of the value of the Coombs test as an aid in the diagnosis and management of congenital hemolytic disease. (See Table I.)

Case 1, Death of Erythroblastotic Infant Prior to Use of Exchange Transfusions.—This Rh-positive infant was born jaundiced of an Rh-negative mother. The Rh antibody status of the mother was not known at the time of delivery but was later found to be positive for blocking antibodies in a titer of 1:16. The jaundice was progressive and marked. At no time was there any appreciable anemia or erythroblastemia. Therefore, simple transfusions were withheld. On the fourth day of life the jaundice was deeper and convulsions occurred. Blood was sent elsewhere for a Coombs test which was reported as 4 plus a few hours before death. The necropsy showed kernicterus. This case exemplifies

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the importance of performing the Coombs test immediately upon the birth of every jaundiced infant.

Cases 2, 3, 4, 5, 6, and 7, Exchange Transfusion Group.—These infants all showed 3 to 4 plus Coombs reactions and were given exchange transfusions within a few hours of the time of birth. One infant died forty-eight hours later, from either cardiac failure or kernicterus. Permission for necropsy was not granted. All of the remaining infants were well six months to one year later with no sequelae. However, a much longer follow-up period is advisable for adequate appraisal of results from the standpoint of possible mental or neurological disturbances. The mothers showed marked variability in their Rh sensitization. The mother in Case 7 showed no agglutinating or blocking antibodies but 2 plus "cryptagglutinoids"[3] were found in her blood with the aid of Coombs serum. The presence of strongly sensitized red blood cells in any newborn infant as demonstrated by a 3 to 4 plus Coombs test performed at birth was considered an immediate indication for an exchange transfusion regardless of the presence or absence of clinical symptoms. Exchange transfusions were done as soon after birth as arrangements could be made, usually within the first few hours. In three of the cases a Coombs test was done on the day following the transfusion and showed a reversal to negative in each instance, indicating fairly complete removal of sensitized red blood cells. Two infants required additional small simple transfusions to overcome the anemia due to continued hemolysis of the remaining sensitized erythrocytes which replacement transfusion failed to remove.

Cases 8, 9, 10, 11, and 12, Group in Which Exchange Transfusion Was Not Performed.—Cases 8, 9, and 10 were similar in that jaundice was noted within twenty-four hours of birth and the Coombs test was negative. The impression was early icterus neonatorum rather than mild hemolytic disease. Case 11 developed slight jaundice at 24 hours but no anemia or erythroblastemia. Because of the 2 plus Coombs test, it was felt that this child could be followed expectantly. The infant recovered without specific treatment. Case 12 showed slight jaundice at 6 to 12 hours but no anemia or erythroblastemia. Inasmuch as the jaundice did not increase, exchange transfusion was not done although the child had a 3 plus Coombs test. Only one simple transfusion was needed to overcome a mild anemia which appeared later.

Cases 13, 14, 15, 16, and 17, Group With O-A-B Incompatibility.—A negative Coombs test was obtained in all of these infants. Treatment was conservative and recovery was the rule. Case 17 required no transfusions, whereas Case 15 was given more than one simple transfusion with group-specific A and B substances added. Four of the cases occurred in primigravida.

Cases 18, 19, and 20, Miscellaneous.—In the first two cases the Coombs test was of value in the differential diagnosis. Case 18 was an infant born jaundiced about the face, groin, and umbilical cord. Moderate anemia was present. The probable etiology was hemorrhage from premature separation of the placenta. Erythroblastosis was considered unlikely when the Coombs test was reported negative and there was no group or Rh incompatibility. Case 19[4] showed icterus neonatorum on the fourth day and a routine blood count revealed 21 per cent

TABLE I*

	MOTHER															
NO.	CRAV-IDA	PARA	TYPE	RH	ANTI-RH	ANTI-A OR ANTI-B	JAUN-DICE	HGB	RBC	WBC	NOR-MBL†	TYPE	RH	COOMBS	TREATMENT	REMARKS
1	iii	ii	AB	neg.	1-16	—	at birth	130	5.0	18,000	1/100 WBC	B	pos.	4 plus	None	Died on fourth day with kernic-terus
2	ii	i	AB	neg.	1-256	—	3 plus in 5 hours	60	2.26	44,700	56,000	—	—	4 plus	Exchange transfusion	Died in 48 hours
3	ii	i	O	neg.	1-8	—	3 plus in 12 hours	60	3.44	53,000	13,500	A	pos.	4 plus	Exchange transfusion and 1 transfusion	Recovered
4	iii	ii		neg.	1-4	—	1 plus	124 100	5.25 3.6	21,500	7,000	O	pos.	3 plus	Exchange transfusion	Recovered
5	ii	ii	A	neg.	1-64	—	3 plus at birth	82	3.75	41,000	10,000	A	pos.	3 plus	Exchange transfusion	Recovered
6	ii	i	A	neg.	1-1,000	—	2 plus in 12 hours	84	3.9	24,000	1,600	O	pos.	3 plus	Exchange transfusion	Recovered
7	vi	iv	A	neg.	cryptag-glutin-ins 2 plus	—	1 plus in 3 hours	88	3.94	12,500	750	O	pos.	3 plus	Exchange transfusion and 2 trans-fusions	Recovered
8	iii	ii	—	pos.	—	—	3 plus in 18 hours	132	5.5	11,000	13,600	A	pos.	neg.	None	Recovered without treatment
9	ii	i	—		—	—	1 plus in 10 hours	122	6.15	38,000	3,500	A	pos.	neg.	None	Recovered without treatment
10	ii	i	O	neg.	neg.	—	1 plus in 24 hours	130	4.8	21,000	2,500	—	neg.	neg.	None	Recovered without treatment

11	iii	ii	O	neg.	1-8	—	1 plus in 24 hours	118	5.2	13,500	1,500	—	pos.	2 plus	None	Recovered without treatment
12	ii	i	O	neg.	1-8	—	1 plus in 6-12 hours	120	5.0	19,500	1,000	O	pos.	3 plus	1 transfusion	Recovered with one transfusion
13	i	0	O	neg.	neg.	Anti-A 1-640	3 plus in 12 hours	124	4.0	23,000	3,500	A	pos.	neg.	1 transfusion	Recovered with one transfusion
14	i	0	O	CD†	—	Anti-A 1-320	1 plus in 6 hours	108	3.9	36,000	11,000	A	CD†	neg.	1 transfusion	Recovered with one transfusion
15	i	0	O	pos.	—	Anti-A 1-512	1 plus in 4 hours	140	6.6	17,600	4/100 WBC	A	pos.	neg.	2 transfusions w. A&B subst.†	Recovered with two transfusions
16	i	0	O	pos.	neg.	Anti-A 1-512	4 plus in 6 hours	80	3.5	25,400	5,000	A	pos.	neg.	1 transfusion w. A&B subst.†	Recovered with one transfusion
17	iii	i	O	neg.	—	Anti-B 1-1024	1 plus in 3 hours	104	4.2	23,000	12,000	B	pos.	neg.	None	Recovered without treatment
18	i	0	O	pos.	—	—	2 plus at birth	80	3.9	32,000	3,500	O	pos.	neg.	None	Anemia due to premature separation of placenta
19	iii	ii	O	pos.	neg.	—	Fourth day	140	6.5	11,500	3/100 WBC	O	pos.	neg.	None	21% myeloblasts. Leucemoid reaction
20	ii	i	O	pos.	neg.	—	none	118	5.1	16,800	none	O	pos.	neg.	None	Hemolytic anemia pregnancy; Baby not affected

*A few omissions of pertinent data were due to circumstances beyond our control.
†Normbl = normoblasts.
CD = Rh subtype.
A&B subst. = A and B group specific substances.

myeloblasts. Many additional blood counts all demonstrated a leucocytosis with about the same number of primitive cells. By the third month, the infant's blood picture returned to normal and the episode was thought to be a leucemoid reaction. Hemolytic disease was excluded by a negative Coombs test on the infant, a negative Rh antibody titer in the mother, and no incompatibility of blood types. Case 20 is that of a normal infant delivered of a mother who had an acquired chronic hemolytic anemia of pregnancy. The mother's blood showed no Rh antibodies and no circulating hemolysins by the technique of Dameshek and Schwartz,[5] but her washed erythrocytes showed 3 plus clumping with Coombs serum. The newborn infant was normal in every respect and the Coombs test was negative. The hemolytic disease in the mother disappeared soon after delivery. The positive Coombs test in the mother indicated that a hemolytic antibody of some kind existed in her blood. Apparently it had not been transmitted to the infant.

DISCUSSION

The primary objective for the effective management of congenital hemolytic disease of the newborn infant is to rid the involved infant of immunologically altered erythrocytes and circulating foreign antibody as soon as possible after birth. Immediate replacement or exchange transfusion serves these purposes. Whether exchange transfusion has any effect on antibody which is already fixed in tissue cells is still debatable. However, further tissue damage is minimized by early removal of foreign circulating antibody.

The problem in the past has, therefore, been the proper selection of cases of congenital hemolytic disease for exchange transfusion. The height of the mother's Rh antibody titer is not always correlated with the severity of the disease in the infant. This is shown by our series of cases. However, many infants are born with no evidence, either clinical or hematologic, of erythroblastosis, and develop signs of the disease rapidly after several hours or even days. In our limited experience, which is in agreement with that of others,[6] the Coombs test is best correlated with the degree of the disease process in the Rh-sensitized infant. It has fulfilled the requirement for a rapid, simple, and reliable test which can be employed at birth on cord or infant's blood for the diagnosis of congenital hemolytic disease and for consideration of proper therapy.

Until more is known about the prevention of residua of erythroblastosis, it seems advisable to use exchange transfusions in borderline as well as in manifest cases. Some infants with strongly positive Coombs tests have recovered without such transfusions, as in Case 12, but the wisdom of this procedure cannot be estimated until there has been a long period of follow-up for sequelae.

The results of the Coombs test in erythroblastotic infants with O-A-B incompatibility bears emphasis. The test was negative in all of our cases, which is the opposite of what one finds in Rh sensitization. This fact has helped differentiate cases of suspected sensitization to both O-A-B and Rh factors.

None of our cases of icterus neonatorum gave a positive Coombs test. Even when there was a fall in hemoglobin to below 100 per cent in the newborn in-

fant this was regarded as an exaggeration of the normal neonatal processes of blood destruction and not hemolytic disease due to Rh incompatibility, provided that O-A-B incompatibility could be excluded.

CONCLUSIONS

1. In a series of twenty selected cases, the Coombs (developing) test has proved to be of great value in the diagnosis and management of congenital hemolytic disease of the newborn infant.

2. The results of the test appear to be more closely correlated with the severity of the disease in cases of Rh sensitization than any other finding.

3. The test is very helpful in the proper selection of cases for exchange transfusion.

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THE TREATMENT OF PRURITUS FROM CHICKEN POX WITH PYRIBENZAMINE

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AT A recent meeting several pediatricians expressed interest in our experience with the use of antihistaminics for the relief of itching in chicken pox. The following observation, therefore, may be of some value to those who treat children.

There was an increased incidence of chicken pox in this area during the past season. One of our first patients had very severe itching with the disease. The customary treatment with antipruritic lotion, Aspirin, and sedation gave no relief. It was not long before the mother called and insisted that "something be done." For want of anything better, treatment with Pyribenzamine in elixir* was instituted. Twenty milligrams of Pyribenzamine were given four times daily. After two or three doses, the child obtained complete relief from itching. A week or so later, another patient with complaint of severe itching complicating chicken pox was given similar treatment and also experienced relief within a short time. Since that time Pyribenzamine has been routinely prescribed as part of the symptomatic treatment for every patient with chicken pox. Over a period of several months, with many new cases appearing every week, we do not recall any child complaining of itching with chicken pox since this type of medication was included. In addition, it seemed that the number of secondary skin infections was materially, if not entirely, reduced.

Although the relief obtained may have been entirely coincidental, it is our impression that the addition of the antihistaminic has been of value. It is doubtful whether the result was obtained by the sedative action which these drugs occasionally effect, since none of the children was especially drowsy. No attempt was made to use the antihistaminic in topical application. Keating and Code[1] have recently shown that the antihistaminic action of Pyribenzamine and other synthetic histamine antagonists is separate from, and not dependent on, their local anesthetic action. Whether chicken pox gives rise to some related histamine reaction in the skin is, of course, speculative, but the apparent relief from itching the Pyribenzamine offered in these patients might suggest this.

The average dose of Pyribenzamine approximated 2 mg. per pound of body weight in twenty-four hours. In the younger children the proprietary elixir was well tolerated. For older patients the 50 mg. tablets were more convenient. An amount sufficient to last the patient only three or four days was

From the Grand Forks Clinic.

*Tripelennamine Hydrochloride, Pyribenzamine hydrochloride elixir, Ciba. Each 4 c.c. (approximately 1 teaspoonful) contains 20 mg. Pyribenzamine hydrochloride.

prescribed in each case. At times a combination of equal parts of Benadryl and Pyribenzamine was used.

No doubt many of the other antihistaminics would work as well. No patient with chicken pox suffered ill effects from the drug. It should be pointed out that the antihistaminic gave no relief to those patients who had painful ulcerated lesions of the oral or vaginal mucosa.

It may be of interest to note that Pyribenzamine gave relief to several children who had pruritis with the rash of measles. However, pruritus was not prevalent in our patients with measles, so that no appraisal could be made.

The antihistaminics have been used successfully for the relief of itching in a number of cases of dermatoses associated with pruritus. A review of recent literature indicates that the use of antihistaminics for the treatment of itching complicating chicken pox has not been reported. No doubt other physicans have offered antihistaminic preparations to patients with chicken pox and may have obtained the same results as reported here. It would be desirable to have this observation substantiated, if possible. All of our patients were treated in the home. Physicians who care for large groups of children in institutions are in the best position to make some type of control study when the opportunity arises.

Fortunately, chicken pox is usually not a serious disease. Nevertheless, in our experience, pustular dermatitis and cellulitis, though infrequent, have at times been dangerous complications. Secondary infections of the skin with *Staphylococcus aureus* and hemolytic streptococcus cause the most severe complications, and may be followed by acute glomerulonephritis. Stokes[2] writes that furuncles, impetigo, staphylococcal or streptococcal septicemia, abscesses, gangrene, and suppurative adenitis may occur as the result of scratching or lack of care in cleansing the skin of the hands. He states that scratching considerably increases the danger of these complications. Therefore, any useful addition to the symptomatic treatment for the relief of itching in chicken pox may help relegate this disease to an even more harmless status.

CONCLUSION

On the basis of recent clinical experience it is suggested that Pyribenzamine (and probably other antihistaminics) given orally, may offer prompt relief from the severe pruritus which often accompanies chicken pox.

Note: Since this paper was written, we have been informed that Pyribenzamine hydrochloride elixir has been replaced by Pyribenzamine citrate elixir, Ciba, 4 c.c. (approximately 1 teaspoonful) containing 30 mg. of Pyribenzamine citrate.

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STUDIES ON THE CHEMOTHERAPY OF VIRUS INFECTIONS

II. Failure of Darvisul (Phenosulfazole) to Affect the Course of Experimental and Clinical Poliomyelitis

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INTRODUCTION

CONSIDERABLE interest was aroused by the announcement early in the summer of 1948 of a newly synthesized sulfonamide compound, Darvisul (phenosulfazole), which was purported to have remarkable prophylactic and therapeutic effects on poliomyelitis produced experimentally in mice. This was later officially reported by Sanders, Subba Row, and Alexander.[1] It was also claimed, although not published, that this drug was effective against human poliomyelitis as well.

The purpose of this communication is to report the failure of this drug in both experimental and clinical poliomyelitis. Since this paper was prepared other reports have been presented recently[2-5] indicating similar negative results in experimentally infected mice but no other clinical trials have been reported to our knowledge.

METHODS

Drug.—The compound, Darvisul, or sodium phenosulfazole, was supplied† in sterile ampules containing a 25 per cent solution for intravenous use and in 0.5 Gm. tablets for oral administration. Chemically it is somewhat related to the well-known sulfonamide drugs but differs in that it is a phenol rather than an aniline derivative. The structural formula was described to us as "N-(2 thiazolyl) 1, 4, phenol sulfonamide." There is no satisfactory method for its determination in blood and body fluids. The Bratton and Marshall method applied to other drugs of the sulfonamide series cannot be utilized here.

Experimental.—Toxicity studies were conducted in mice and maximal, nonfatal doses were determined for mice, CFW strain weighing 10 to 15 Gm. The results of toxicity tests and antibacterial action as compared to that of sulfadiazine are given in Table I. The dosage schedule and treatment plan appears in Table II.

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†We wish to thank Dr. Benjamin Carey of the Lederle Laboratories Division of the American Cyanamid Company for making available to us prompt and generous supplies of the drug which we requested for this study.

TABLE I. BACTERIAL SENSITIVITY TO DARVISUL: TWENTY-FOUR-HOUR GROWTH

ORGANISM	MG. % DARVISUL REQUIRED TO INHIBIT GROWTH
Staphylococcus	313
E. coli	78
Diphtheroid	156
Proteus	625

ACUTE 50 PER CENT TOXICITY (Test Animal: CFW Mice, 10 to 15 Gm.)

	50% TOXIC DOSE	KILLING TIME
Darvisul	1.25 Gm./kilo	12 minutes
Sodium Sulfadiazine	2.60 Gm./kilo	6 hours

TABLE II. EVALUATION OF DARVISUL (PHENOSULFAZOLE) IN EXPERIMENTAL POLIOMYELITIS

TEST ANIMAL: CFW Mice, 10-15 Gm.
DARVISUL THERAPY: 25 m./mouse/day—I. P. in 4 divided doses until death or end of 30-day observation period
VIRUS: LANSING STRAIN: Dose, 1 Ld 50 intracerebrally

	NO. MICE IN GROUP	AVERAGE INCUBATION PERIOD IN DAYS	MICE WITH OBSERVED PARALYSIS	PARALYZED MICE SURVIVING	TOTAL NO. DEATHS	% MICE WITH OBSERVED PARALYSIS	% TOTAL NO. OF DEATHS
Mice begun on treatment five days prior to virus injection	45	10	27	0	38	60	84
Mice treated after virus injection	50	11	17	0	32	34	64
Untreated control mice	50	11	23	0	30	48	60

Virus.—A group of fifty mice were pretreated with the drug for several days, then inoculated with an Ld 50 dose of mouse-adapted Lansing strain poliomyelitis virus and treatment continued until an observation period of thirty days had elapsed.

A second group of fifty mice received treatment and virus simultaneously, while a third group served as untreated controls for comparison of infection rate and mortality. The results appear in Table III.

TABLE III. DRUG REACTIONS OF PATIENTS ON DARVISUL THERAPY

REACTION	NUMBER
Nausea and vomiting	10
Convulsions	
abortive	1
spinal	1
bulbar	2
Anorexia	1
Urinary retention	2 (?)
Rash	2
Total number of patients on Darvisul	68
Per cent experiencing reactions	26

Clinical.—Beginning in July, 1948, and for the duration of the season as cases of poliomyelitis were admitted to the hospital and the diagnosis established, they were separated into four categories: nonparalytic, spinal, corticobulbar, and respiratory. Each of these was listed and numbered consecutively on entry. The odd-numbered were treated and the even-numbered observed

as untreated controls for comparison. The treatment, following essentially the instructions given to us by Dr. Carey of the Lederle Laboratories, consisted of the administration of 0.4 Gm. per kilogram of body weight in glucose or saline by the intravenous route for the first two days, followed by oral administration of the same dose in tablet form for the next three days. Toxic effects of the drug were noted. Except for a larger number of patients with emesis, the reactions were more or less similar to those observed with other sulfonamides. The reactions are listed in Table III. Follow-up of patients of both the treated and control groups consisted of general evaluation, or frequent muscle examination regarding progression of paralysis, lack of change or improvement in the period immediately following institution of therapy and for several weeks to months afterward. The results are presented in Table IV.

TABLE IV. CLINICAL APPLICATION OF DARVISUL IN THE TREATMENT* OF POLIOMYELITIS

TYPE ON ADMISSION	NO.	IMPROVED	PROGRESSED	NO CHANGE	EXPIRED
		Treated			
Nonparalytic	22	3	Spinal 6	12	(Bulbar) 1
Spinal	35	19	Bulbar 1	14	1
Respiratory	3	0	0	3	0
Corticobulbar	8	4	0	3	1
Total	68	26	7	33	3
Per cent		38	10	47	5
		Controls			
Nonparalytic	26	2	Spinal 5 Respiratory 1	18	0
Spinal	31	18	Respiratory 1	12	0
Respiratory	2	0	0	0	(Bulbar) 2
Corticobulbar	10	4	0	4	2
Total	69	24	7	34	4
Per cent		35	10	49	6

*These patients received 0.4 Gm. Darvisul per day, per kilo of body weight, diluted in 5 per cent glucose by intravenous drip for the first two days, and 0.4 Gm. per day kilo of body weight by mouth for three successive days.

CONCLUSION

The data presented above indicate clearly that Darvisul (phenosulfazole), when administered to experimentally infected animals or patients acquiring the disease naturally, has no effect whatever on the course of the infection.

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THE TREATMENT OF POLIOMYELITIS WITH PHENOSULFAZOLE

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DURING the course of a screening program for compounds with antiviral activity, a sulfonamide, N(2 thiozolyl) phenol sulfonamide, named phenosulfazole,* was found to be effective in protecting mice infected with a strain of mouse poliomyelitis virus.[1] It also exerted some inhibiting effect on the propagation of the virus in tissue culture, although no actual destruction of the virus was demonstrable in serum. Since the drug was found to be of low toxicity in animals, a therapeutic trial in acute poliomyelitis in humans was indicated.

When, in August, 1948, phenosulfazole was made available to us, we decided to treat alternate poliomyelitis patients with the drug. During the months of August through November, 1948, we observed sixty-six patients admitted to the Isolation Division of Gallinger Municipal Hospital who had been diagnosed as having acute poliomyelitis. The following criteria were employed for the diagnosis of acute poliomyelitis: (1) a characteristic history, and (2) the presence of muscular weakness and/or the presence of cells in the spinal fluid with a normal dextrose content and negative cultures. Patients admitted after having passed through the acute phase of the disease were not utilized in the present study.

If, on admission, a patient was considered suitable for study as far as diagnostic criteria and activity of the disease were concerned, he was placed in one of two groups by strict alternation without selection. One group received 75 mg. per kilogram of body weight every six hours for the first twenty-four hours, and for a longer period of time in patients with the bulbar form of the disease. This intravenous therapy, during the last twelve hours of the first twenty-four-hour period, was supplemented by phenosulfazole orally at the rate of 150 mg. per kilogram of body weight per day. Subsequent therapy was at the rate of 300 mg. per kilogram of body weight per day by mouth, and was continued until signs of activity had subsided for two to three days. The intravenous doses were prepared by dissolving 10 Gm. of phenosulfazole in 1 liter of isotonic sodium chloride or 5 per cent dextrose solution, using the volume required to obtain the desired dose.

The other group of patients received an intravenous injection of isotonic saline or 5 per cent glucose solution which had been colored with 100 to 200 mg. of Gantrosan† per liter. The two intravenous solutions were indistinguish-

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*Supplied by the Lederle Laboratories Division of the American Cyanamid Company, Pearl Pearl River, N. Y. under the name of Darvisul.

†Supplied by Hoffman-LaRoche Inc., Nutley, N. J.; the chemical formula is 3,4-dimethyl-5-sulfanilamido-isoxazole.

able as to color. Oral placebo tablets were made of dextrose and these two placebos were administered on dosage schedules exactly the same as for phenosulfazole. In an attempt to make the study as objective as possible, two of the other investigators supplied the drug and thus controlled the alternation of cases. Evaluation of the response to therapy was carried out in each case by the investigators, who were not aware of which solution a particular patient had received, and also by the house and visiting staffs, who were not cognizant that a controlled experiment was being attempted.

RESULTS

Phenosulfazole was given to thirty-two patients, while thirty-four patients made up the control group. The patients have been classified according to the type of disease in Table I. Since this classification was made after discharge, it includes all patients who were admitted with, or subsequently developed, paralysis while under therapy, and is not a reliable guide as to the quality of the groups on admission.

TABLE I

CONTROL SERIES		PHENOLSULFAZOLE SERIES	
No. patients	34	No. patients	32
Classification			
Bulbar spinal	3	Bulbar spinal	4
Bulbar	1	Bulbar	1
Spinal	9	Spinal	13
Nonparalytic	21	Nonparalytic	14

Certain clinical and laboratory data obtained on admission are given in Table II. This table emphasizes the similarity between the two groups of patients, in spite of the wide range of variation within the disease itself.

TABLE II. DATA OBTAINED ON ADMISSION IN PATIENTS TREATED WITH AND WITHOUT PHENOSULFAZOLE

	CONTROL SERIES	PHENOSULFAZONE SERIES
Age (years)		
Mean	16.0	16.0
Range	1-37	1-36
Duration of Illness Before Admission (days)		
Mean	3.7	3.5
Range	1-8	½-10
Initial Temperature (degrees F.)		
Mean	101.6°	101.5
Range	99-104.2°	98.8°-104°
Initial Cerebrospinal Fluid Findings		
Leukocyte count (per cu. mm.)		
Mean	148	143.8
Range	3-800	13-390
Polymorphonuclears (per cent)		
Mean	35.0	40.0
Range	6-92	0-90
Polymorphonuclears (absolute number)		
Mean	89.2	76.0
Range	2.0-632.0	0-255
Protein (mg. per 100 c.c.)		
Mean	71	99.2
Range	31-121	35-251

In an attempt to find criteria that would be useful in deciding the effectiveness of phenosulfazole, the following were selected: progression of, or development of, paralysis after the start of therapy, and the duration of fever over 101° F. There was one fatal case in each group. In the treated series, death occurred in a 25-year-old white female admitted on the fourth day of her illness. After the paralysis, which was of the Landry type, had spread rapidly, the patient died on the second hospital day. Death apparently was due to involvement of vital medullary centers. The patient in the control group who died was a 17-year-old white female. Death took place in a respirator on the eighth hospital day. Post-mortem examination revealed almost complete atelectasis of all lung tissue.

TABLE III

	CONTROL SERIES	PHENOSULFAZOLE SERIES
Paralysis present on admission	11	15
Progression after twelve hours of therapy	2	2
Progression after twenty-four hours of therapy	9 (5)*	16 (4)*
Deaths	1	1
Duration of fever over 101° F. (hr.)		
All cases		
Mean	27.9	48.8
Range	8-104	16-336
Uncomplicated cases		
Mean	26.1	28.3
Range	8-104	16-144
Duration of fever over 100° F. (hr.)		
All cases		
Mean	28.5	49.5
Range	8-116	16-336
Uncomplicated cases		
Mean	29.4	27.5
Range	8-116	16-144

*The figures in brackets represent cases in which muscle weakness was noted by the orthopedic or physiotherapy staff after the acute process had subsided.

The case record of each patient was evaluated as to the presence or absence of muscular weakness on admission. Further evaluation of the progression of muscular weakness was made at the end of twelve hours and again twenty-four hours after therapy had been instituted (Table III). It can be seen that progression was more frequent in the treated than in the untreated group, as determined by the house officers as well as by the final muscle check. As shown in Table III, the duration of fever for the entire experimental group was longer than for the entire control group, although when fever caused by obvious complicating bacterial infection is eliminated, the duration was practically identical for the two groups.

For the purpose of studying the toxic effects of phenosulfazole, we have included six patients who were treated by us at Gallinger Hospital and elsewhere, and who were not included in the investigational series. Among the entire group of seventy-two patients, no toxic effects from phenosulfazole were observed except mild nausea in some cases when the drug was being given intravenously. This could usually be controlled satisfactorily by decreasing the rate of flow. Four of seven patients who received a second course of the drug orally complained of slight nausea only.

SUMMARY AND CONCLUSION

1. Phenosulfazole was given to thirty-two patients with acute poliomyelitis in strict alternation with thirty-four patients who were observed as controls. The two groups were comparable with regard to the duration of the illness, the presence of paralysis, and the cerebrospinal fluid findings on admission.

2. There was no appreciable difference in the outcome in the two groups.

3. No toxic effects were observed in the patients treated with phenosulfazole.

4. It is concluded that phenosulfazole has no effect upon the clinical course of acute poliomyelitis.

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SUBLUXATION OF THE ATLANTO-AXIAL JOINT: SEQUEL TO INFLAMMATORY PROCESSES OF THE NECK

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INTRODUCTION

THE type of atlanto-axial subluxation associated with infections of the tissues of the neck occurs almost exclusively in children, yet has received little attention from pediatricians, who are usually first consulted when the condition occurs.

Experience with four children seen at The New York Hospital with this syndrome and a review of the literature have demonstrated that difficulty in making this diagnosis frequently delays treatment for many months or even years.[1] A particularly confusing factor is the roentgenogram, since routine views frequently do not reveal minor subluxations.[1, 2] The selectivity of this condition for the pediatric age group, the paucity of reported cases in the pediatric literature, and recently developed techniques in diagnosis have prompted the present report.

CASE REPORTS

CASE 1.—M. J. G., a 6½-year-old white girl, was admitted to The New York Hospital in October, 1937, with the chief complaint of a stiff neck of four weeks' duration. Her family history was negative. She had had the usual childhood diseases and also removal of the tonsils and adenoids, but had otherwise been well.

Three weeks before admission she had rhinorrhea and a mild productive cough. Two weeks before admission she awoke with a painfully stiff neck which persisted despite hot gargles, heat, and massage prescribed by a private doctor. She was seen in the out-patient department here where a roentgenogram of the cervical spine showed an anterior subluxation of the atlas on the axis, and the child was admitted for treatment.

Physically she was a well-developed, well-nourished child. Her head was turned toward the left and was tilted toward the right shoulder; the chin was depressed forward. The head was held rigidly in this position; jarring or any motion of the neck was painful. There was tenderness of the left side of the neck and over the first (axial) spine. The pharynx was red and there were palpable anterior and posterior cervical lymph nodes. The neurological examination was negative.

Laboratory studies showed the urine to be negative and the white blood cell count to be 12,400 per cubic millimeter with a leucocyte differential count of 24 per cent lymphocytes, 4 per cent monocytes, 4 per cent eosinophiles, and 68 per cent polymorphonuclear cells.

The patient was placed in skeletal traction by means of a chin halter for fourteen days when x-ray examination showed reduction; a plaster neck jacket was then applied for forty-seven days. The end result was satisfactory functionally and cosmetically.

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CASE 2.—F. M., a 9-year-old white boy, was admitted to The New York Hospital in September, 1945, with the complaint of stiff neck for two months. His family history was unremarkable. He had had a right purulent otitis media at the age of 5 years and a tonsillectomy and adenoidectomy at the age of 7½ years.

Two months before admission, the patient received an injection of pertussis vaccine in the right arm, and within a few hours developed malaise, fever, and a moderate local reaction. The next day he awoke with a mild torticollis which became progressively worse and more painful until he could not walk without complaining of pain. No history of trauma or infection could be elicited. Three weeks before admission he was seen in the out-patient department of this hospital, where several diagnoses were considered, including myositis, radiculitis, meningitis, atypical poliomyelitis, tetanus, retropharyngeal abscess, cerebellar tumor, fracture, and dislocation. Roentgenograms of the cervical spine taken with routine views were reported as negative. Physiotherapy was given without relief. The patient was then admitted for diagnosis and treatment.

Physical examination revealed a well developed, well nourished, 9-year-old white boy whose head was tilted toward the left shoulder and turned toward the right; this position was rigidly maintained and the patient complained of pain with any active or passive motion of the head. There was tenderness on the right side of the neck and just below the occiput. On changing position, such as sitting up from a recumbent position, he protected his head with his hands. The ears, pharynx, mastoids, heart, lungs, and abdomen were negative; there was no lymphadenopathy and the sternocleidomastoid muscles were normal.

Laboratory examinations showed a negative urine examination, Mazzini test, and Mantoux test. The white blood cell count was 9,700 per cubic millimeter. The differential count was normal.

Stereoscopic x-ray views of the cervical spine were taken and reported as negative. However, because the torticollis was so painful, skeletal traction by means of a chin halter with 5 lb. of force was applied with the neck in hyperextension. Meanwhile, review of all roentgenograms showed "definite malalignment and over-riding of the facets on the right side . . . while on the left the usual joint space is visualized." After eighteen days of skeletal traction with the chin halter no improvement was evident, so that patient was taken to the operating room for reduction of the subluxation by manipulation under general anesthesia. Traction was put on the neck, which was then deviated to the side opposite the subluxation (left), the neck and head were then rotated in the direction of the affected side (right). On the third manipulation, a definite "snap" was heard and passive movement was free in all directions. A plaster neck jacket was then applied for a period of ninety-five days, and then removed. The results were excellent, and no further difficulty occurred in a two and one-half year follow-up.

CASE 3.—B. S., a 9½-year-old white girl, was admitted to The New York Hospital in June, 1947, with the complaint of painful torticollis and fever of four days' duration. Her family history was negative. She had had a tonsillectomy at the age of 5½ years. That night she developed a wry neck and was placed in a plaster cast for a two-week period with a good therapeutic result.

Ten days before admission, the patient developed an upper respiratory infection. Four days before admission she had muscular aches, chills, and fever of 105° F. and developed a painful torticollis. She was treated for two days with sulfadiazine without response.

Examination revealed an acutely ill, well-developed and well-nourished girl complaining of pain in her neck. The neck was rotated to the left and the head flexed forward, depressing the chin; active or passive motion of the neck elicited exquisite pain. The pharynx was red and there was a purulent postnasal discharge. The nasal mucosa were also inflamed. Anterior and posterior cervical lymph nodes were palpable bilaterally. There was pain and tenderness on the right side of the neck and over C_1 and C_2 posteriorly. There was a bulge in the posterior pharyngeal wall. The sternocleidomastoid muscles were unremarkable. The rest of the examination was unremarkable.

A white blood cell count on admission was 21,000 per cubic millimeter with 80 per cent polymorphonuclear leucocytes. Mazzini and Mantoux tests were negative.

There was disagreement among the radiologists who interpreted the x-ray films of the cervical spine taken by routine technique. An orthopedic consultant interpreted these x-rays as showing a unilateral anterior subluxation on the right.

The patient was placed in skeletal traction with Crutchfield tongs imbedded into the skull. Two days later she was found apneic and cyanotic, but responded to stimulants and artificial respiration. She was diplopic and stuporous for several hours afterward. The tongs were reimbedded one inch forward to afford greater extension of the neck and maximum patency of the airway. The respiratory infection was treated with parenteral penicillin. Eight days after admission the upper respiratory infection became worse and was complicated by a left otitis media; the pharyngeal bulge was suspected by a consultant as being a subsiding retropharyngeal abscess. Her course was further complicated by an occipital decubitus ulcer.

After twenty-one days of skeletal traction, the tongs were removed and a plaster neck jacket applied. Roentgenograms of the cervical spine at this time were negative. She was discharged from the hospital to be followed in the clinics; three months later the cast was removed and roentgenograms were again negative. There was a full return of flexion, extension, abduction and rotation to the left, but rotation to the right was limited to 45° and there was still some tenderness over C_1 and C_2 on this side.

Case 4.—D. M. This 8-year-old white girl was admitted to The New York Hospital in October, 1947, with the complaint of painful torticollis of four months' duration. Her father and a brother had hay fever, and the paternal grandfather and an uncle had diabetes. The patient was also known to suffer from hay fever but otherwise her past history has been unremarkable.

Four and one-half months before admission the patient had a sore throat and fever to 104° F.; she was treated by a private doctor with sulfonamide drug and bed rest for ten days. After the drug was discontinued she developed a hot, tender swelling on the right side of the neck which reached its maximum three weeks later. It was painful and the child was noted to keep her head turned to the left and flexed forward. There was no history of trauma. A private doctor made a diagnosis of "mumps" and disregarded the torticollis.

Three and one-half months before admission she took a trip by train and it was noted that the vibration and jarrings of the ride were extremely painful, so that she protected her head with her hands. She was seen by another private doctor and a pediatric consultant who made a diagnosis of "virus infection." An x-ray examination of the cervical spine at this time was interpreted as negative. Physical therapy was given to the neck daily. The swelling subsided completely two months before admission but the painful torticollis persisted. She was admitted to this hospital for diagnosis and treatment.

Examination revealed a well-developed, well-nourished girl who complained of pain in the right side of the neck with any motion; the head was rigidly turned to the left and slightly forward, depressing the chin. There was pain on lateral flexion, flexion and extension of the neck, rotation past 45 degrees to the left and past the midline to the right, pressure on top of the head, and raising the head off the neck. There was tenderness over C_1 and C_2 on the right and posteriorly. A bulge was palpable in the posterior pharyngeal wall. The sternocleidomastoid muscles were normal. In changing position, she held her head in her hands to protect against sudden movement in the neck. The remainder of the examination was unremarkable.

Routine x-ray views of the cervical spine including those through the open mouth were reported as negative by the radiologists. However, an orthopedic consultant made the diagnosis of nontraumatic subluxation of the atlantoaxial joint on the right. Skeletal traction by chin halter with the neck in hyperextension was started and continued for seventeen days, when it was discontinued during the day because of marked symptomatic improvement, but within five days pain and torticollis returned and continuous skeletal traction was resumed. Because the chin halter was so uncomfortable, it was decided to use Crutchfield tongs; this was done forty-one days after skeletal traction was started by chin halter, and was continued for thirty days more. A plaster cast was applied to immobilize the neck in hyperextension and the patient was discharged to be followed in the out-patient department. Three months later the cast was removed; there was no discomfort and function was normal except for slight limitation of rotation to the left.

GENERAL CONSIDERATIONS

A. Synonyms of this condition appearing in the literature.—

Distensionsluxation (Wittek).[3]
Drehungsverrenkung (Sudek).[4]
Inflammatory dislocation (Fitzwilliams).[5]
Maladie de Grisel (Desfosses).[6]
Non-traumatic subluxation (Berkheiser and Seidler).[2]
Spontaneous dislocation (Hess).[1]
Spontaneous hyperemic dislocation (Watson-Jones).[7]
Torticollis nasopharyngien (Grisel).[8]

B. Definitions.—

Atlas: The first cervical vertebra is a ring of bone with short transverse processes, but no body or spine. The anterior portion of the inner aspect of the ring has a shallow groove which forms a joint with the ventral part of the odontoid process. The anterolateral masses of the ring support the facets of the atlanto-axial joints. The superior facets are oval, concave, and support the occipital condyles. The inferior facets are flat and oval, and slant downward, laterally and slightly forward.[2, 9]

Axis: The second cervical vertebra has two small transverse processes, a heavy spinous process, and a forward shaft of bone called the odontoid process. The superior facets are flat, oval, and slant downward and laterally.[2, 9]

Atlanto-axial joint: There are four distinct joints between the first and second vertebrae, two of which are related to the odontoid process: the atlanto-odontoid joint, a rotary diarthrosis between the anterior aspect of the odontoid

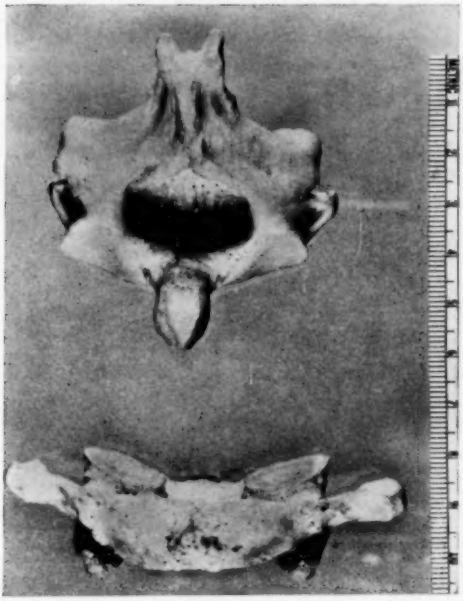

Fig. 1.—Posterior views of the atlas and the axis showing the inclination and flatness of the facets.

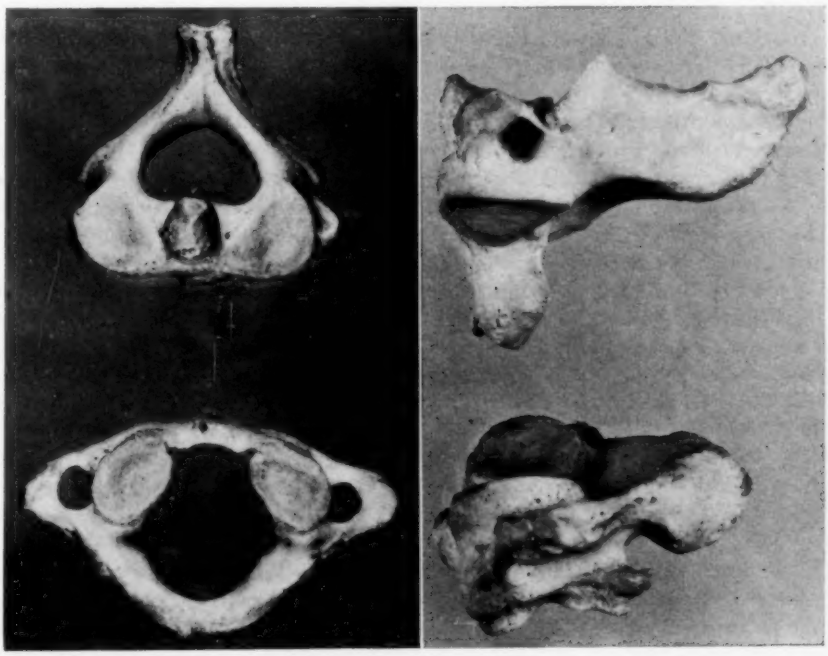

Fig. 2.—Further views of the atlas and the axis showing the nature of their articulating surfaces.

process and the posterior aspect of the anterior arch of the atlas, and the syndesmo-odontoid joint between the posterior aspect of the odontoid process and the transverse ligament. The two lateral arthroidal diarthroses (gliding joints) are the ones with which we are mainly concerned.[9, 10] They have loose capsules which allow maximum motion,[9] much of which is rotation (of the neck) but also some lateral movement.[11]

Dislocation: A disarrangement of the bones entering into the formation of a joint; luxation.[12]

Subluxation: A minor degree of dislocation; an incomplete luxation or dislocation.[12]

Transverse ligament: A heavy ligament attached to the anteriolateral portions of the ring of the atlas and forming the posterior support of the odontoid process.[9]

Details of the anatomy of these two vertebrae are apparent in Figs. 1 and 2. These views clearly demonstrate the flatness and the slanting of the lateral articulations.

REVIEW OF LITERATURE

The earliest case of atlanto-axial subluxation associated with infection of the neck was reported by Bell in 1830.[13] His patient had a pharyngeal ulcer and died of respiratory failure; post-mortem examination revealed erosion of the transverse ligament and subluxation of the atlas on the axis resulting in pressure on the cord.

In 1903, Böger[14] described a case of unilateral dislocation of the atlanto-axial joint in a 17-year-old boy with acute rheumatic fever. He believed that the arthritic process had loosened the joint ligaments sufficiently to allow this dislocation.

Wittek,[3] in 1908, reported the case of an 11-year-old boy who developed a subluxation of this joint subsequent to periostitis of the jaw. He presumed that the joint ligaments had been stretched, "probably due to a metastatic effusion into the joint between the odontoid and the anterior atlas ring on one side and between the odontoid and the crucial ligaments on the other side, and also in the inferior articulations between the atlas and the axis."

Jacobs,[15] in 1918, accepted Wittek's theory of "metastatic effusion into the atlanto-axial joint" and compared this type of subluxation with that seen occasionally in cases of typhoid fever complicated with subluxation of the hip. He stressed the threat of cord injury in dislocation of the atlas, especially when it was associated with a fracture of either of the first two cervical vertebrae.

Swanberg,[16] in 1919, reported the case of a 22-year-old soldier who developed painful torticollis following a tonsillectomy. He thought that the transverse ligament of the axis had ruptured, releasing the posterior odontoid support thereby predisposing the joint to subluxation.

Sudek,[4] in 1923, thought the etiology in one of his cases to be excessive passive rotation of the neck while under deep anesthesia for an operation on the neck.

Greig,[17] in 1931, suggested that hyperemia due to the adjacent inflammatory process caused decalcification of the vertebrae, especially about the ligamentous attachments, thereby relaxing the ligaments of the joint. Leriche and Policard[18] demonstrated this principle experimentally, showing the decalcification of bone with increased blood supply, and its sclerosis with ischemia.

Watson-Jones[7] presented roentgenographic evidence of this mechanism in 1931. His patient was a 9-year-old boy who developed torticollis as a complication of acute mastoiditis; the lateral view of a roentgenogram of the cervical spine failed to reveal the anterior arch of the atlas but showed subluxation of this joint. Three months later, when the infection had subsided, the anterior arch was again calcified. Watson-Jones postulated that the decalcification had loosened the ligamentous attachments of the joint, facilitating avulsion of the transverse ligament without fragmentation of the atlas.

Grisel,[8] in 1930, proposed the theory that irritative contracture of the suboccipital and paravertebral muscles following cervical lymphadenitis due to a nasopharyngeal infection caused the subluxation. Tedesco, Grisel, Desfosses, and Tassin[19] published the first report on the subject in a pediatric journal in 1930.

Berkheiser and Seidler[2] in 1931 favored Wittek's theory of metastatic effusion into the joints and added that the anterior and posterior bursae were involved in and contributed to the predisposition to subluxation. They pointed out that the forward position of the center of gravity of the head and the forward slanting of the facets predisposed this joint to forward subluxation.

Hess and associates[1] in 1935 concluded that the "production of the atlanto-axial dislocation involves a combination of factors, the *sine qua non* being weakening of the lateral ligaments. Spasm of the cervical muscles in association with loose ligaments is a feasible mechanism. Nevertheless, it appears more likely that the dominant role played by the spasm is the prevention of spontaneous and easy reposition, with resulting locking of the overlapping edges."

Brav[20] in 1936 reported an interesting case of voluntary subluxation of this joint by a 29-year-old man who used this peculiar ability for illegal gain.

SYMPTOMS AND FINDINGS

Typically with this condition there will have been an inflammatory process in or about the neck, most frequently in the nasopharynx, from one day to several weeks before the onset of the torticollis.[1, 2] When the torticollis starts during the acute phase of a severe cervical infection, it is frequently presumed to be due to protective spasm until this symptom persists after the acute process recedes. The subluxation may have been precipitated during sleep,[21] following a sharp jar as a slap on the back[22] or throwing a baseball,[23] or during passive motion of the neck under anesthesia.[24] This type of subluxation is very painful and is aggravated by jarring or sudden movement of the head so that the patient limits his activity and protects his head with his hands when changing position.[1, 2]

The symptoms depend upon the type of subluxation present, three types of which are possible: anterior unilateral, anterior bilateral, and posterior unilateral. Posterior bilateral subluxation of the atlas on the axis is theoretically impossible in the presence of an intact odontoid process and transverse ligament.[2]

Patients with anterior unilateral subluxation present the following picture: the neck is rotated away from the subluxated side; the head is tilted toward the affected side and flexed anteriorly so that occasionally the mouth cannot be opened sufficiently to allow palpation of the nasopharynx; this position is rigidly maintained. In some instances the shoulder on the affected side may be elevated. A nasal quality of the voice has been described with this condition and is thought to be related to the partial obliteration of the nasopharynx by the anterior arch of the atlas, which is displaced forward and can be palpated as a bulge in the posterior pharyngeal wall.[1] Tenderness is palpable over the subluxated joint laterally and posteriorly over C_1 and C_2.[25] The spinous process of the axis is frequently palpable away from the midline toward the affected side (Sudek's sign)[4] due to the counter-rotation of this vertebra. The rotation of the atlas and axis in opposite directions results in detectable cervical scoliosis.[1, 2] Root and cord signs have been infrequently reported with this syndrome. However, Wilson[26] reported a case of a 62-year-old woman with unilateral atlanto-axial subluxation following an upper respiratory infection who developed quadriplegia and other neurological symptoms which were completely relieved by skeletal traction. Woltman[27] described the case of a 14-year-old boy who developed an anterior unilateral subluxation as a sequel to pharyngitis and six months later sustained a bilateral anterior subluxation complicated by numbness and weakness of the extremities following a fall. Immobilization by cast relieved the symptoms.

In patients with a posterior unilateral subluxation, the neck is rotated toward the affected side, Sudek's sign is positive on this side, and there is no pharyngeal bulge.[1, 2]

If anterior bilateral subluxation is present, there is little or no rotation of the neck, the head is tilted forward, motion is markedly limited in all directions, and the pharyngeal bulge is most prominent.[2]

Patients with this syndrome have been reported from 2 to 62 years of age. Wilson[26] reviewed twenty-eight acceptable cases and found that 85.6 per cent of patients were under 13 years of age. An analysis of fifty-six cases including those reviewed and those reported here, shows that 76.8 per cent of patients were under 13 years of age; the average age was 12.2 years.

Of fifty-two acceptable cases of nontraumatic subluxation of the atlanto-axial joint, including those reviewed and those reported here, 46 per cent occurred in male and 54 per cent in female patients. The average age was 13.0 years for male and 11.6 years for female patients.

X-RAY DIAGNOSIS

A consideration of the use of x-ray in this condition is most important since so frequently the routine x-ray film is reported as negative when indeed

a subluxation exists as judged by symptoms and examination and is demonstrable by special x-ray techniques. Swanberg[16] reported the case of a 22-year-old soldier who had had six roentgenograms of the neck for persistent torticollis, all of which were reported negative; the condition remained undiagnosed for six months. Swanberg (1919) stated, "this is the second case of anterior dislocation of the atlas I have observed that has not been recognized by the roentgenogram." Since this complaint in 1919 the same thought has been repeatedly reiterated in the literature on this subject. At The New York Hospital at least two cases of subluxation of this joint, undiagnosed for more than one year, have been seen, in which several x-rays were reported as negative.

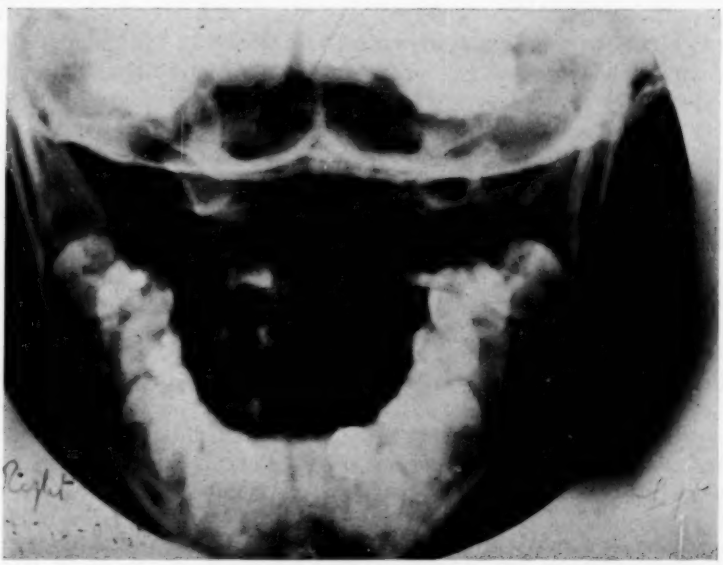

Fig. 3.—A reproduction of an x-ray view in the anteroposterior position through the opened mouth showing unilateral subluxation on the right. Note the shortening of the facets on the affected side with displacement of the odontoid process to the opposite side.

Technically, this joint is difficult to study roentgenographically.[2, 23] The routine examination includes the anterioposterior view through the open mouth and lateral views. The former is more important in mild subluxations, but when the chin is depressed forward sufficiently to interfere with opening of the mouth, it is difficult to obtain. Lateral views frequently show no abnormality since displacement of the atlas is minimal in this type of subluxation.[29]

Stereoscopic views are preferred, especially in children whose immature bony structures may have appearances which mimic fractures due to the numerous ossification centers and areas of incomplete fusion.[28]

The Morgan Meter[30] is occasionally useful. It utilizes the formula: Intensity × Exposure Time = Constant. It is also useful for x-ray views through plaster casts as well as for deep structures.

Jostes[31] (1942), reporting results with the laminograph described by Dr. Sherwood Moore[32] and Mr. Keiffer of Connecticut, stated that "the cervical vertebrae can be studied and understood roentgenographically only by means of this body section method." He states further that this usually discloses dislocations of the occipito-atlas and atlanto-axial joints missed by other techniques. He presents photographic evidence to substantiate his contention. His interest in the use of the laminograph started after he saw several patients with persistent neck pain with negative routine cervical roentgenograms who responded therapeutically to skeletal traction and who showed minor changes by the laminograph. Dr. Moore had previously stated that "upper cervical traumas and anomalies are a bane of the radiologist when he is limited to conventional methods or stereoscopic films from different angles; there is a need for something additional. This is fulfilled by the laminograph."

In the positive roentgenogram in the anterioposterior view through the open mouth, there is reduction or disappearance of the joint space on the affected side, often with overlapping of the facets. There may be some lateral displacement of the odontoid process. In the lateral view there may or may not be detectable anterior displacement of the body of the atlas.[1, 29]

TREATMENT

Subluxation of the atlanto-axial joint is sometimes susceptible to treatment by manipulation under anesthesia by the method of Walton,[33] in which the neck is hyperextended, its tilt and rotation exaggerated, and as traction is applied to the head with countertraction to the shoulders, the head is slowly rotated toward the midline. This method does not always reduce the subluxation and may be dangerous in inexperienced hands or in the presence of a fracture or avulsion of the transverse ligament. Reduction by manipulation should be followed by immobilization in a leather collar or plaster neck jacket.

In most cases, however, permanent results will require a skeletal traction in hyperextension by means of a chin halter or Crutchfield tongs imbedded in the skull. Elevation of the head of the bed by shock blocks makes use of gravity for countertraction. Hyperextension of the neck may be effected by use of a second mattress atop the first so placed that the head falls over one end of the upper one as the patient lies supine. Skeletal traction is continued until clinical and x-ray evidence of subluxation disappear; this varies from two to four weeks. Following reduction by manipulation or traction, immobilization in the reduced position is secured by a plaster cast, Thomas collar, or similar device.[1, 2, 29] Bisgard[34] (1932) described a device for the simultaneous traction and complete immobilization of the cervical spine.

Some authors report spontaneous subluxation followed by spontaneous reduction. Swanberg's case was suspended by the head, using the body's

weight for the traction force after manipulation under general anesthesia had failed; this attempt also failed and continuous skeletal traction had to be employed.

In cases with neurologic symptoms, skeletal traction alone is usually adequate treatment, though cord decompression may be necessary.[35, 36]

Gillette[37] reported cases of nontraumatic torticollis improved by tonsillectomy.

SUMMARY OF REPORTED CASES OF NONTRAUMATIC SUBLUXATION OF THE ATLANTO-AXIAL JOINT CONSIDERING AGE, SEX, AND ASSOCIATED INFLAMMATORY PROCESS

AUTHOR	YEAR	AGE (YR.)	SEX	INFLAMMATORY PROCESS
Berkheiser and Seidler[2]	1931	9	F	Influenza
Blunch[39]	1935	10	M	Fever
Brookes and Ewerhardt[41]	1932	19	F	Tonsillar abscess
Chesterman[42]	1936	10	F	Tonsillitis
Desfosses[6]	1930	7	F	Nasopharyngitis
Englander[43]	1942	7	F	Tonsillitis and adenitis
Enrique Rivarola[44]	1938	8	M	Cervical abscess
		15	?	Otitis media
Frank[45]	1931	9	M	Retropharyngeal abscess
Fitzsimmons[46]	1915	8	F	Pharyngitis and adenitis
Fitzwilliams[5]	1934	10	M	Coryza and adenitis
Garcia-Diaz[47]	1940	9	F	Cervical abscess
Gillette[37]	1896	3	?	Cold
Grisel[8]	1930	8	F	Tonsillitis
		9	F	Nasopharyngitis
Hauflig and Schlosberg[48]	1940	7	M	Nasopharyngitis and adenitis
Hess and associates[1]	1935	6	M	Scarlet fever and adenitis
		11	F	Coryza
Heikkla[49]	1937	17	M	Parotitis
Jacobs[15]	1918	5	M	Fever
Llambia[50]	1940	10	F	Nasopharyngitis
Martin[51]	1942	6	M	Mastoiditis and adenitis
Maxwell[52]	1947	10	F	Pharyngitis and cervical adenitis
Piotet[53]	1934	8	F	Retropharyngeal abscess
Sudek[4]	1923	8	F	Pharyngitis and adenitis
Swynghedauw, Bonte and Laine[54]	1942	10½	F	Otitis media
		8	F	Cervical adenitis and fistula
Watson-Jones[7]	1931	16	F	Tuberculous adenitis
		2	?	Pharyngitis
		9	M	Mastoiditis
Wilson and associates[26]	1940	62	F	Upper respiratory disease
Weissberg and Reinstein[55]	1940	52	M	Coryza
Wittek[3]	1908	11	F	Alveolar abscess
Woltman and Meyerding[27]	1934	14	M	Tonsillar abscess
Zeilter and Odessky[56]	1934	12	F	Parotitis and influenza
Dennison[57]	1939	5½	M	Following mastoidectomy
Fitzsimmons[46]	1915	11	F	Following mastoidectomy
Jones[58]	1931	10	M	Following tonsillectomy
Martin[51]	1942	6	M	Following mastoidectomy
Maxwell[52]	1947	14	M	Following mastoidectomy
		6	F	Following mastoidectomy
Odelberg-Johnson[59]	1932	16	F	Following tonsillectomy
Steele[60]	1937	7	M	Following adenoidectomy
Swanberg[16]	1919	22	M	Following tonsillectomy
Tedesco and associates[19]	1930	11	F	Following mastoidectomy
		12	F	Following mastoidectomy
Berkheiser and Seidler[2]	1931	8	F	Acute rheumatic fever
Böger[14]	1903	17	M	Acute rheumatic fever
Ely[61]	1911	13	M	Acute rheumatic fever
Evans[62]	1941	9	M	Acute rheumatic fever
Fitzwilliams[5]	1934	15	M	Acute rheumatic fever
Foxe and Friedman[63]	1930	35	M	Chronic rheumatoid arthritis

PROGNOSIS

In unilateral subluxation, the prognosis is good with adequate treatment. Without treatment, the patient's appearance may be markedly affected. Hess and associates,[38] in a five-year follow-up of one of their original cases in which treatment had been refused, found moderate asymmetry of the face, rotation of the head, prominence of the infraoccipital muscles, limitation of motion of the neck, and a positive Sudek's sign. The mouth, which had previously been impossible to open, could now be opened fully. Incidentally, this patient had been seen by several physicians and a chiropractor who doubted the diagnosis because of a negative history of trauma.

There are two reports in the literature of anterior unilateral subluxation being converted into anterior bilateral subluxation following moderate trauma; both of these patients developed symptoms of cord compression which, though not fatal, were incapacitating.[25, 27] However, the proximity of this joint to the respiratory center of the medulla increases the hazard of this syndrome. Though the episode of apnea, cyanosis, and later diplopia in Case 3 remains unexplained, one wonders if it was not due to compression of the medulla.

SUMMARY AND CONCLUSIONS

1. Nontraumatic subluxation of the atlanto-axial joint is not a frequent occurrence, but is an important cause of persistent torticollis in the pediatric age group.

2. It is usually preceded by an infection in the tissues of the neck, including coryza, pharyngitis, pharyngeal abscess, cervical adenitis and abscess, otitis media, mastoiditis, parotitis, etc.

3. The mechanism of subluxation appears to be related to metastatic effusion into the joint causing distention and relaxation of the capsule and joint ligaments; subluxation is precipitated by spasm of the paravertebral muscles, minor trauma, or passive manipulation as in anesthesia or sleep.

4. Three types of subluxation occur: (a) anterior unilateral, (b) posterior unilateral, and (c) anterior bilateral.

5. Common symptoms are: pain and tenderness over the subluxated joint, worse with jarring and rigidity of the neck. In the anterior unilateral type, the chin is depressed and the neck is rotated away from the subluxated side. There is a pharyngeal bulge and Sudek's sign is present on the opposite side. In posterior unilateral subluxation, the head is tilted toward the subluxated side, there is no pharyngeal bulge, and Sudek's sign is present on this side. In the anterior bilateral type, the head is held more or less rigidly close to the midline, the chin is depressed, Sudek's sign is negative, and there is a marked pharyngeal bulge.

6. Neurologic symptoms are unusual, and when present, bilateral subluxation or fracture of the odontoid process must be considered.

7. X-ray visualization of this region is not dependable by routine methods. A negative report does not preclude the absence of a subluxation.

8. Prognosis for recovery is good for function and facial symmetry if treated early and adequately.

9. Treatment consists of manipulation under general anesthesia or skeletal traction with the neck in hyperextension followed by immobilization with a plaster cast or leather collar.

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LIPOID NEPHROSIS COMPLICATED BY HOMOLOGOUS SERUM JAUNDICE

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THIS report deals with a case of a child with clinically pure lipoid nephrosis who died from homologous serum jaundice during a period of remission. Since plasma has been used extensively in the treatment of the nephrotic syndrome, this combination may become increasingly frequent.

A. B., a 3-year-old white female child, entered the Children's Division of the Cook County Hospital on Nov. 12, 1946, with a history of insidious onset of edema and ascites approximately one month in duration. She had been perfectly well except for measles and chicken pox during the first year of life and pertussis during the second year. There was no history of an antecedent illness, either of a chronic or acute nature, which may have precipitated the disease.

On physical examination the child showed the characteristic appearance of a nephrotic with a moderate amount of generalized pitting edema, ascites, and pallor. There were no other significant physical findings except for a palpable, nontender liver. The urine showed 4 plus albumin, specific gravity 1.034, acid reaction, no sugar or acetone, no blood to chemical or microscopic test, and a few pus cells in the centrifuged sediment. The complete blood count was within normal limits, with a hemoglobin concentration of 13.5 Gm. (Sahli), and a red count of 4.41 millions. The total serum protein concentration was reduced to 4 Gm. per 100 c.c. with reversal of albumin-globulin ratio; the nonprotein nitrogen was 37 mg. per 100 c.c. The sedimentation rate was 30 mm. per hour (Wintrobe). The Kahn test was negative.

The clinical course (Fig. 1) showed a progressive increase in edema and ascites until the seventy-third hospital day, when weight loss began. At various times during the first half of her hospital stay (from the tenth to the fifty-third day), the child received infusions of concentrated pooled human plasma with no appreciable change in her edema. She was given one-half of a Mercupurin suppository on the thirty-first, thirty-seventh, and fiftieth hospital days with little effect. On the fifty-third hospital day, one-half cubic centimeter Mercupurin injected intravenously caused a transient weight loss of 1.5 pounds. From the seventy-eighth to the eighty-fourth hospital day, salt-poor human albumin was injected daily in amounts of 25 to 35 c.c. The subsequent weight loss was rapid and pronounced. However, there was a mild diuresis prior to the institution of this therapy, and it cannot be stated with certainty that the response was produced by the therapy. On the eighty-fifth day, at which time the child appeared edema-free, the total proteins had risen to 5.1 Gm. per 100 c.c.

The liver remained enlarged during the entire hospital stay, but not tender. Just prior to her hospital discharge, the cephalin flocculation was 0

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and the thymol turbidity 5.3. The blood pressure was occasionally moderately elevated, 130/85 on the sixty-eighth hospital day, and 112/78 on the eighty-fourth hospital day. However, the significance of such occasional deviations from the normal is questionable, particularly as the child was fearful of blood pressure determinations. Urea clearance tests showed 95 per cent of normal on the twenty-ninth hospital day, and 100 per cent on the thirty-third hospital day.

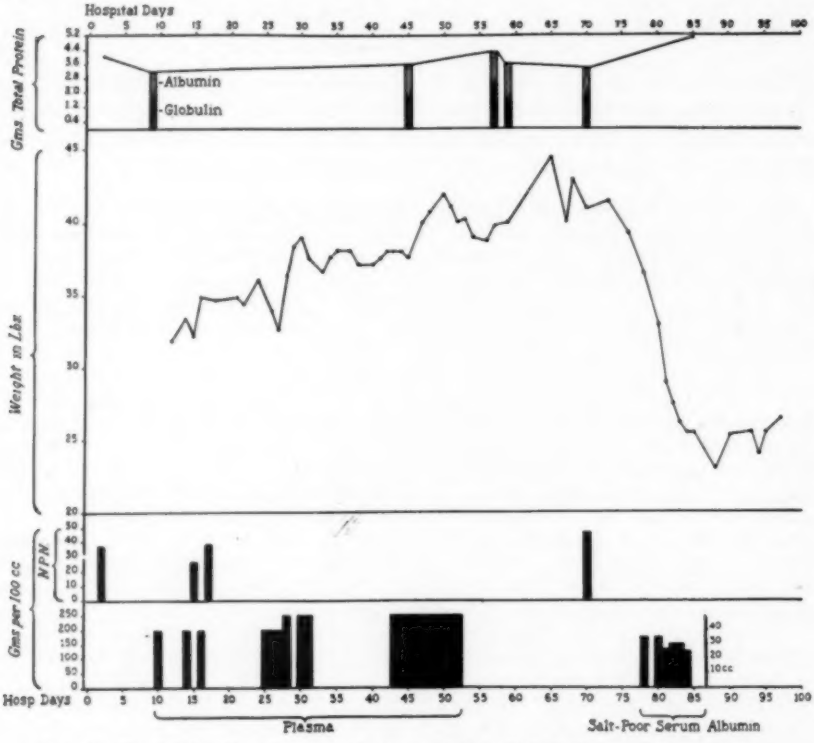


Fig. 1.—Chart indicating the clinical course of the child during first hospital stay.

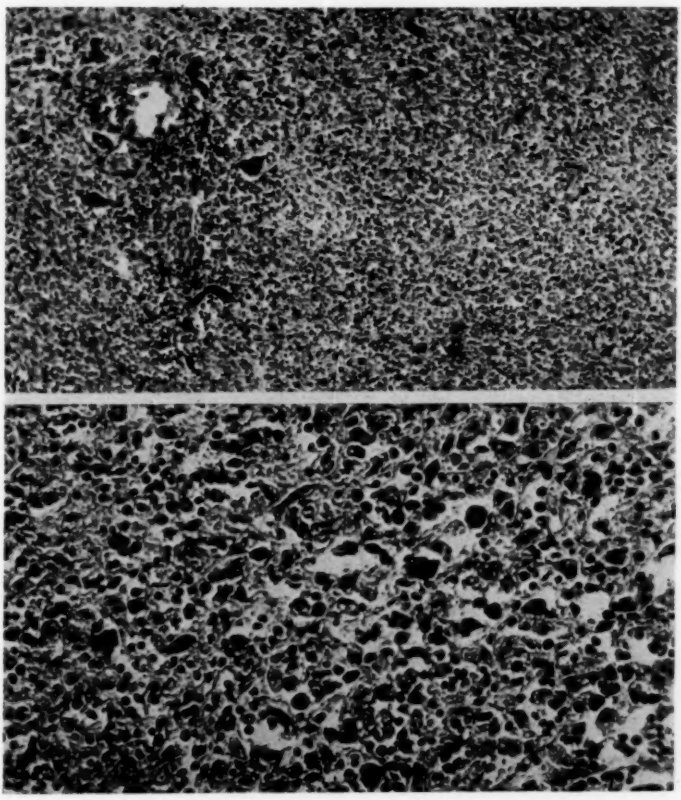
On the ninety-seventh hospital day, the twenty-fourth-hour urine specimen showed only 270 mg. albumin. At no time during her hospital stay or in subsequent clinic visits did her urine show blood, using the benzidine and orthotolidine tests. On one specimen, an occasional red cell was noted in the centrifuged urine. The nonprotein nitrogen remained consistently within normal limits except for a finding of 46 mg. per 100 c.c. on the seventieth hospital day, at which time the anasarca was close to its maximum.

Subsequent to release from the hospital on the ninety-eighth day after admission, this child was seen in the Clinic on Feb. 28, 1947, and March 28, 1947, in excellent condition. Her weight remained stationary, slightly above that on discharge from the hospital. It was felt that the slight increase could be ascribed to improved nutrition. Her blood pressure was 110/60 on February 28, and 105/60 on March 28. Urine showed one plus albumin and occasional white but no red cells.

On April 6, 146 days after her first admission, the child was again brought to the hospital. This time she was comatose, and markedly jaundiced, but showed no edema. She vomited considerably. She had been febrile for one week, and had been taking a sulfa medication for five days. Four days prior to admission her urine became brown and her skin yellow. A few hours after admission to the hospital the patient died.

Autopsy.—The peritoneal cavity contained approximately 50 c.c. of a sanguineous, yellow fluid. The lungs were dark purple-red, congested, and edematous. The pleura revealed multiple ecchymoses. Trachea and bronchi contained some sanguineous, mucopurulent material. The heart was of normal size, the myocardium pale, the mitral valve edematous. The purple-blue spleen weighed 75 grams and was of reduced consistency. The architecture on the cut surface was somewhat obscured.

A.



B.

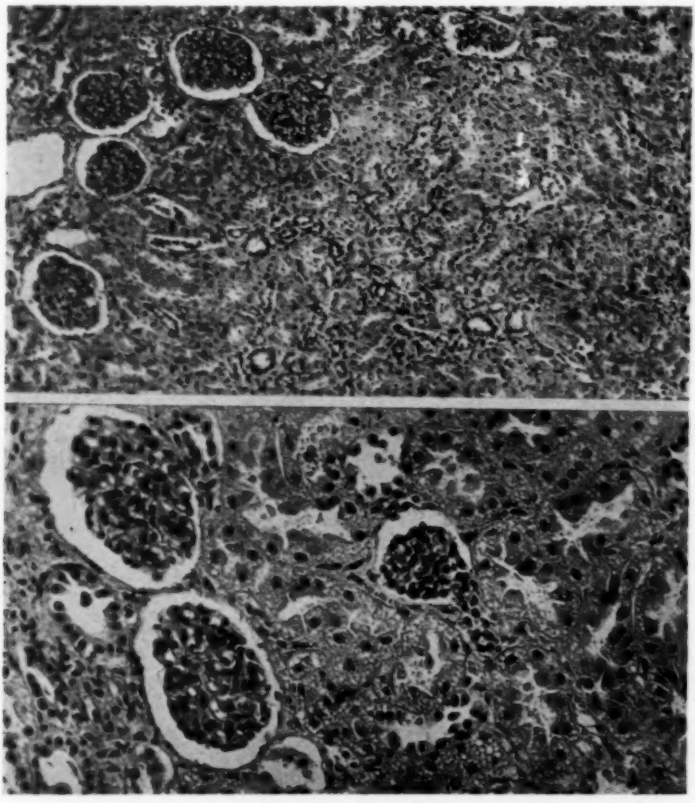
Fig. 2.—Photomicrograph of liver revealing fulminant infectious hepatitis.

A, Low-power view. The central veins are closer to the portal triads than normal. The liver cells are missing, except for cords mostly near the portal triads which resemble proliferated bile ducts. The lobular framework is crowded by histiocytic elements. There is dense cellular infiltration of the portal triads.

B, High-power view. In the lobular framework, no liver cells are seen but many mononuclear cells, the larger of which contain bile pigments and phagocytosed material.

Histologically, the large follicles had small germinative centers; the pulp revealed marked reticulum and endothelial cell hyperplasia. The pale pink liver weighed 550 grams. Its inferior edge was sharp. The consistency was unusually low and the organ flattened out if placed on a table. The architecture was mostly obscured; only in circumscribed areas was it well preserved or even exaggerated due to a distinct red color of the lobular centers. The histologic structure of the liver cell cords was entirely missing. However, the arrangement of the central and peripheral fields was well preserved although the fields were closer to each other than usual (Fig. 2, *A*). The liver cells within the lobules were almost entirely missing. Only toward the periphery were a few isolated polygonal liver cells seen, which revealed diffuse coagulation necrosis of the cytoplasm and occasionally small fat droplets. On the lobular periphery

A.



B.

Fig. 3.—Photomicrograph of kidney of child dying about two months after remission of clinically established "pure" lipoid nephrosis.

A, Low-power view. The architecture is intact. The cell content of the glomeruli appears normal. Some albuminoid granules are found in the lumen of the tubules.

B, High-power view. There are some focal adhesions of glomerular loops with proliferation of the pericytes. Fine vacuoles (after fat extraction) are noted on the base of the epithelial cells of the proximal convoluted tubules.

liver cells were arranged in irregular cords which often revealed a wide bile capillary in their center. These cords simulated proliferated bile ducts. The meshes of the intralobular connective tissue framework were crowded with mesenchymal cells, the larger of which revealed a superficial similarity to liver cells. They contained granular bile pigment and phagocytosed cell fragments. In addition, smaller mononuclear cells were seen, such as lymphocytes and histiocytes. The segmented leucocytes were mostly eosinophilic (Fig. 2, *B*). In the portal triads and to a lesser degree around the central vein, there was a dense infiltration of similar, round, cellular elements, many of them pigment carrying. The slightly dilated sinusoids contained a moderate number of red cells. A few were also seen in the tissue spaces. The reticular fiber framework was intact; in a few places it was collapsed but nowhere scarred. The widened gall bladder bed was edematous. The portal lymph nodes were markedly enlarged and revealed extensive reactive hyperplasia. Pancreas and lipoid-rich adrenals revealed no abnormalities. The pale pink-gray kidneys were large, weighing together 150 grams. Their surface was smooth. On the cut surface the markings were well recognized. Histologically the architecture was intact (Fig. 3, *A*). The glomeruli revealed, in general, normal cell content. Only occasionally some glomerular loops appeared matted together and were surrounded by a continuous layer of small cells with dark nuclei in palisade arrangement (Fig. 3, *B*). The pericytes appeared in places proliferated; nowhere however, did the endothelial cells show proliferation. The basement membrane was mostly normal although in some loops it appeared thickened and the hematoxylin-eosin sections appeared diffusely red. In MacGregory or glycoprotein stains, such loops revealed a double contour of the basement membrane. The tubular epithelium was normal except for regularly arranged, fine vacuoles (apparently after dissolution of fat) on the base of the epithelium of the proximal convoluted tubules (Fig. 3, *B*). There was no albuminous material in Bowman's space but some in the tubular lumen in form of densely staining granules. Vessels and interstitial tissues were normal. Urogenital and gastrointestinal tracts revealed no changes. Examination of the head was not permitted.

DISCUSSION

This case is of interest for two reasons: first, to record the pathologic findings in a case of lipoid nephrosis in a state of remission; and second, to add to the limited series recorded[1, 2] one additional case of fulminant viral hepatitis in a child as a result of plasma administration (homologous serum jaundice).

The first problem presented by this case is the morphologically unimpressive renal lesion which obviously must be related to the clinical picture of the lipoid nephrosis. It appears clear that what has been originally lumped together under the name "nephrosis" by Volhard and Fahr should be subdivided into two conditions. One reveals primary involvement of the tubular apparatus, often on the basis of an intoxication, such as with mercury. It is best called toxic or necrotizing nephrosis and characteristically is associated with functional impairment of the tubular apparatus. Uremia and hypertension are the usual findings. The second is characterized by excessive albuminuria, hypoproteinemia, hypercholesteremia, and lipid deposition in the renal tissue. This type is not necessarily associated with uremia, hypertension, and impaired renal function. Functionally, the basic defect appears to be a pathologically

increased permeability of the glomerular loops to both serum proteins and lipids. This is associated with the morphologic picture of a thickened basement membrane of the glomerular loops. The anatomical changes of the tubules, namely, fatty metamorphosis and albuminoid swelling, have no functional significance.

The nephrotic syndrome as a clinical entity has been exhaustively studied[9, 14, 19] and its various clinical and biochemical features are well known. Whether this distinctive clinical syndrome is the manifestation of a stage in the course of a glomerulonephritis[8] or of several fundamentally different diseases[11-13] is a controversial subject. There is no doubt that some nephrotic patients show unquestionable evidence of chronic glomerulonephritis[20, 21] and may die in uremia, and that in these cases the nephrotic syndrome is a stage in the course of the glomerulonephritis. It is also well known that others exhibiting the nephrotic syndrome do not show the usual findings of nephritis,[11] the hematuria, azotemia, and hypertension. These latter are the cases that are clinically called pure lipoid nephrosis and it is in this group that recoveries are most frequently reported, particularly since the advent of antibiotics and chemotherapy.

On prolonged observation it has been found that patients exhibiting the nephrotic syndrome generally show bouts of hematuria and often have transitory episodes of hypertension and azotemia, making it increasingly difficult to separate from the syndrome the so-called pure lipoid nephrosis. It has also been observed that many patients with supposed "lipoid nephrosis" later show pronounced nephritic symptoms and die in uremia. It has been stated that these patients develop a secondary, superimposed nephritis.[27] It seems more logical to postulate that there is but one underlying disease[8] and that lipoid nephrosis is an early, perhaps reversible, stage of a chronic glomerulonephritis. This is essentially the conclusion of Ellis, Evans, and Wilson[10, 22] who, in their new and valuable classification, consider it a stage of hydremic or Type II nephritis. In the few autopsy records available of patients dying during the "pure" stage of lipoid nephrosis, glomerular changes are usually reported[11, 14-18] and only occasionally have they been missed.[11, 12, 14, 16, 17]

The presented case offers the opportunity to observe a quiescent case. During the fully developed stage (up to two months before death), there were the typical findings of the "pure" nephrotic syndrome without hematuria azotemia, hypertension, or impairment of renal function. Several months later, after a death not related to renal disease, few scattered adhesions between glomerular loops and some focal thickening of the basement membrane are found. Both can be considered a residue of a preceding glomerular inflammation. The small fat droplets on the base of the epithelial cells of the proximal convoluted tubules are typically found in the fulminant form of infectious hepatitis[4] and thus not related to the previous renal condition. In general, the findings in this case support the viewpoints of those who claim the nephrotic syndrome is a stage in the evolution of glomerulonephritis, a stage in which pathologically increased permeability of the glomerular loops for proteins is the predominating feature.

The second problem presented by this case is that of homologous serum jaundice, or hepatitis, which has come into prominence in recent years with the popular use of pooled plasma or serum.[23, 24] While attention has been focused on the disease chiefly by its high incidence in military personnel, the extensive use of these biological products on infants and children has also made this disease a pediatric problem.[1] However, reports on homologous serum hepatitis in infants and children are still rather meager, and most of the reported cases are very severe or fatal.[25, 26] The long incubation period often makes it difficult to relate the acute illness to the previous administration of plasma or serum. The characteristic clinical syndrome is that of acute onset, fulminating course, with vomiting, jaundice, coma, and shock. The presented case ran the typical fulminating course.

Histologically, the liver presents all the characteristics of the condition which previously has been called acute yellow atrophy, and which Lucké and Mallory[4] recently described as a fulminant stage of epidemic hepatitis. The main characteristics are the rapid, almost explosive death of the epithelial cells simultaneously with a marked mesenchymal reaction, characterized by intralobular and portal infiltration by histiocytic elements. Histologic examination on an extensive material on adults has revealed characteristic differences between the form of acute hepatic necrosis, described by Lucké[3] and Lucké and Mallory,[4] which is caused by viral infection, and a second form with slow cell death which is usually produced by hepatotoxic substances. Such a division into viral and toxic forms is also possible in children[6] and the presented case is an example of the viral form. The viral form, developing as a result of administration of plasma or material contaminated with plasma, is usually more severe than the naturally occurring type, and has a long incubation period ranging from two to eight months, in the present case being from 93 to 136 days. The incubation period cannot be more exactly determined since it is obviously unknown as to which plasma sample was contaminated. Fatalities from this condition are being reported with increasing frequency, and suggest caution in the use of plasma in children as well as in adults.

SUMMARY

The clinical and pathologic findings on a 3-year-old girl, who developed fatal fulminant infectious hepatitis from the administration of plasma as treatment for a clinically "pure" lipoid nephrosis, are described. The plasma was administered four and one-half months before death, and the remission occurred two months before death. The only significant histologic renal alterations were scattered adhesions of the glomerular loops with focal thickening of the basement membrane.

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THE CEPHALIN-CHOLESTEROL FLOCCULATION TEST IN INFANTS AND CHILDREN

With Evaluation of a Microtechnique

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THE need for pediatric standards for the cephalin-cholesterol flocculation test has been stated by current authors. When Krautman introduced his microtechnique utilizing capillary blood,[1] he offered a procedure practicable for pediatric use. It has been the purpose of this study to evaluate this microtechnique further and to determine the normal reactions for pediatric patients.

MATERIAL AND METHODS

The patients examined were the admissions to Children's Hospital and to the newborn nursery of the Starling-Loving Hospital, College of Medicine, Ohio State University.

In the initial phase of this study parallel tests by the technique of Hanger,[2] utilizing venous blood, and by the microtechnique, utilizing capillary blood, were made on all patients, including those with clinical evidence of liver disease. Patients who were examined ranged from 3 days to 15 years in age. Diagnoses included the gamut of admissions to a pediatric hospital, from orthopedic surgery to gastroenteritis.

The second phase of the study included only patients who showed no clinical evidence of liver disease. The microtechnique alone was used in the study of additional patients for this phase. In addition to the patients tested at Children's Hospital, thirty-five determinations were run on newborn infants at Starling-Loving Hospital. Of these, twenty-nine were drawn within twenty-four hours of birth.

Outlines of the two techniques follow:

Hanger Technique as Modified by Neefe and Reinhold.[3]—

Reagents: (1) Cephalin-cholesterol stock antigen;* (2) cephalin-cholesterol antigen emulsion; and (3) isotonic saline solution.

Technique: To 0.2 c.c. of fresh serum, add 3.8 c.c. of normal saline, and 1 c.c. of cephalin-cholesterol antigen emulsion. Mix gently and incubate at room temperature in a dark cabinet for forty-eight hours. Read at twenty-four and forty-eight hours.

Microtechnique of Krautman as Modified by Us.—

Reagents: (1) Cephalin-cholesterol stock antigen: add 5 c.c. of reagent ethyl ether to one unit of Difco antigen. This will keep indefinitely if refrigerated at 0° C.

(2) Cephalin-cholesterol antigen emulsion: the standard technique of preparation of the antigen emulsion as outlined by Hanger was used for both techniques. To 35 c.c. of freshly distilled water heated to 65° to 70° C., add dropwise with stirring 1 c.c. of the stock antigen suspension. Evaporate at 85° to 95° C.

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*Cephalin-cholesterol antigen was obtained from the Difco Laboratories, Inc.

until the volume is reduced to about 30 c.c. Cool; make to exactly 30 c.c. with freshly distilled water. This antigen emulsion is stable for about one week if kept in a dark cabinet at room temperature.

(3) Alkaline normal saline solution: in a 500 c.c. volumetric flask, dissolve 4.25 Gm. of sodium chloride (C.P.) in 150 c.c. of distilled water. Add 17 c.c. of N/50 sodium hydroxide and make to volume with distilled water. This solution is stable, especially if refrigerated.

Technique: Place 1 c.c. of alkaline saline solution in a plain 15 c.c. centrifuge tube. Draw exactly 20 c.mm. of capillary blood, blow blood from pipette into the saline, and mix by shaking. The finger and the lancet must be free of alcohol. As soon as possible centrifuge the suspension to precipitate the red cells and decant the supernatant solution into another centrifuge tube. To this supernatant add 0.1 c.c. of the antigen emulsion, mix gently without inversion, stopper with a cotton plug, and incubate at room temperature in a dark cabinet. Read at twenty-four and forty-eight hours.

Interpretation: In a completely negative reaction the emulsion remains in homogeneous suspension. A moderate flocculation which remains in suspension or settles out with little clearing of the supernatant solution indicates a trace or one-plus reaction dependent upon the amount of flocculation. Marked flocculation with settling, associated with partial clearing of the supernatant solution, indicates a two-plus to three-plus reaction. A water-clear supernatant solution indicates a four-plus reaction.

A wide variation in the subjective interpretation of the turbidity of the supernatant fluid was observed with different technicians. To decrease this variation a turbidometric adaptation was introduced.

Standards are prepared by adding 0.2 c.c. of the antigen emulsion to 2 c.c. of alkaline saline solution; 1 c.c. of this is removed, and twofold, fourfold, and eightfold dilutions are prepared. These dilution standards correspond to the minimum turbidity of the supernatant fluids from negative, one-plus, two-plus, and three-plus reactions, respectively. Clearer supernatant fluid indicates a four-plus reaction. Fresh standards must be prepared with each series of tests.

In reading the determinations the amount of flocculation is noted at the end of forty-eight hours. The flocculant material is then precipitated by high-speed centrifugation for five minutes and the supernatant emulsion decanted. In our practice, comparison of the turbidity of the test sample and the standards was made with a Coleman Spectrophotometer, model No. 11, using a PC-4 filter at 445 mu. For this instrument it was necessary to dilute samples and standards to 6 c.c. for reading. The dilution factor which is necessary will vary with the comparator which is used for the measurement of turbidity.

Although this adaptation was used principally with the microtechnique, it is equally applicable to the standard cephalin-cholesterol flocculation procedure.

RESULTS

The first phase was the evaluation of the microtechnique by parallel testing and an analysis of the problems encountered. The second phase was the collection of normal values.

Evaluation of the Microtechnique.—At the present time it is believed that the cephalin-cholesterol flocculation is dependent upon a quantitative and qualitative variation in the albumin fraction in relation to the globulin fraction of the serum.[4, 5] Because whole blood is drawn for this determination, it was suggested that variations in hematocrit would alter the results by varying the absolute quantity of serum used for the test. Therefore, simultaneous determinations

using 10, 15, 20, 25, and 30 c.mm. of whole blood were run on six patients whose hemoglobins varied from 7.8 to 11.7 Gm. (Table I). Variation at either extreme occurred in two-thirds of the cases but showed no consistent pattern of deviation. Five additional patients under treatment for megaloblastic anemia with hematocrits of 24 to 36 per cent showed no abnormal results.

TABLE I. DILUTION FACTOR IN CEPHALIN-CHOLESTEROL FLOCCULATION TEST

CASE	HEMOGLOBIN (GM.)	CUBIC MILLIMETERS OF WHOLE BLOOD USED IN TEST				
		10	15	20	25	30
		REACTIONS				
118	11.7	1+	1+	1+	1+	1+
119	7.8	2+	1+	1+	1+	1+
125	11.5	–	2+	2+	2+	1+
172	8.1	1+	2+	2+	2+	2+
175	9.7	1+	1+	1+	1+	1+
176	11.7	1+	±	±	±	1+

Variation in the sensitivity of the antigen emulsion with age has been emphasized by many authors. Results of tests on 201 normal sera are presented in Table II. Statistically there is significant correlation between the increasing age of the antigen and the per cent of completely negative reactions. There is no significant increase in plus-minus reactions, and one-plus reactions show a significant degree of variation on one occasion only. There is no significant increase in the number of abnormal responses obtained with increasing age of the antigen emulsion.

TABLE II. RELATION OF AGE OF ANTIGEN TO ANTIGEN SENSITIVITY

Age of antigen (in days)	1	2	3	4	5	6
No. cases studied	50	46	48	22	27	8
Reactions (per cent of cases)						
Negative	26.0	10.9	4.2	0.0	3.7	0.0
Plus-minus	30.0	39.1	14.6	31.8	29.6	50.0
One plus	42.0	39.1	75.0	59.2	59.3	50.0
Two plus	2.0	10.9	6.2	4.5	7.4	0.0
Three plus	0.0	0.0	0.0	4.5	0.0	0.0

Delay in the separation of the red cells from the supernatant diluted serum will result in false positive reactions if that delay is too great (five to six hours). No instance of this is known to have occurred in the present series although it is our impression that the absence of negative reactions among the newborn infants may be due to such a delay. Due to geographical factors a delay of from one to two hours was invariably encountered before separation of the supernatant fluid could be accomplished in this series of tests.

Difficulty in interpretation of the minor changes of turbidity associated with one-plus and two-plus reactions was noted with both tests. For this reason, the turbidometric technique previously described was adopted.

Occasional reactions were seen which interfered with interpretation. The more frequent type resembled a serum clot surrounded by clear fluid. The clot involved the emulsion and showed no evidence of flocculation. This occurred in 8 of 288 determinations (2.8 per cent). The other type revealed precipitation of a part of the emulsion on the walls of the centrifuge tube without true floccu-

lation or clearing of the supernatant fluid. This occurred in three of 288 tests (1.0 per cent). When reactions of these types occur, the determination must be rerun.

Comparison of Microtechnique With Modified Hanger Technique.—A total of 111 parallel determinations were made. Tests in which both techniques gave results of zero to one plus, or from two plus to three plus, were considered to be in satisfactory agreement. On this basis 104 tests (94.5 per cent) correlated (Table III). In six of the seven cases which failed to agree, the microtechnique gave a more positive result. In the remaining case, the Hanger technique, using serum forty-eight hours old, was more positive. A summary of the six patients involved, including diagnoses and the results of earlier or subsequent tests, is included in Table IV.

TABLE III. RESULTS OF PARALLEL TESTING BY HANGER AND BY MICROTECHNIQUES*

		HANGER TECHNIQUE				
		0	±	+	++	+++
MICRO-TECH-NIQUE	0	12	3	3		
	±	6	14	1		
	+	6	21	25	*1*†	
	++	*1*		*4*	9	1
	+++			*1*	2	1

*One hundred and eleven determinations.

†Italicized numbers indicate cases where agreement of the two tests was considered to be unsatisfactory.

TABLE IV. SUMMARY OF CASES IN WHICH STANDARD AND MICROTECHNIQUES FAILED TO AGREE

PATIENT	DIAGNOSIS	AGE	DATE	STANDARD	MICRO
P. S.	Enteritis	3 mo.	10/25	1+	2+
J. B.	Megaloblastic anemia	9 mo.	10/16	2+	1+
			10/25	1+	1+
J. M.	Hydronephrosis	12 mo.	10/12	2+	3+
			10/18	1+	2+
			10/27	—	1+
M. L.	Cellulitis of the leg with purpura	11 yr.	10/12	1+	3+
			10/16	0	2+
			10/17	—	2+
M. G.	Observation for rheumatic fever	13 yr.	10/25	1+	2+
R. K.	Atresia of the bile ducts	5 mo.	10/30	2+	2+
			11/ 8	—	2+
			11/19	1+	2+

This degree of correlation would appear to be sufficient to accept the microcephalin-cholesterol flocculation as a valid method, especially useful in pediatric institutions. The evidence suggests that no positive reactions will be missed, although occasional false positive reactions will be encountered.

Evaluation of Results in Patients Clinically Free of Liver Disease.—Eighty-three determinations involving seventy-eight patients were done by the modified Hanger technique. The results are presented in Table V. Of the tests, only two (2.4 per cent) showed flocculation greater than one plus. One of these tests was run on serum forty-eight hours old; the other test involved a hydrocephalic patient.

Two hundred one determinations, involving 189 patients, done by the microtechnique are summarized in Table VI. Of these, twelve tests (6.0 per cent) showed greater than one-plus flocculation. Repeat determinations, when pos-

TABLE V. RESULT OF CEPHALIN-CHOLESTEROL FLOCCULATION TEST BY HANGER TECHNIQUE IN PATIENTS CLINICALLY FREE OF LIVER DISEASE*

	AGE					
	1-13 WEEKS	3-12 MONTHS	1-3 YEARS	3-6 YEARS	6-10 YEARS	OVER 10 YEARS
Reactions						
0	2	1	1	3	10	6
±	0	5	7	5	8	9
+	2	6	3	3	3	7
++	0	2	0	0	0	0

*Eighty-three determinations on seventy-eight patients.

TABLE VI. RESULTS OF CEPHALIN-CHOLESTEROL FLOCCULATION TEST BY MICRO-TECHNIQUE IN PATIENTS CLINICALLY FREE OF LIVER DISEASE*

	AGE						
	0-5 DAYS	1-13 WEEKS	3-12 MONTHS	1-3 YEARS	3-6 YEARS	6-10 YEARS	OVER 10 YEARS
Reactions							
0	0	3	5	1	2	8	3
±	10	7	9	8	7	8	8
+	23	11	17	19	7	10	23
++	2	0	3	1	1	1	3
+++	0	1	0	0	0	0	0

*201 determinations on 189 patients.

sible, were within normal limits in all cases. These false positive reactions occurred in a wide variety of conditions (Table VII) without apparent explanation.

On the basis of these determinations, the previously accepted standard for adults for the cephalin-cholesterol flocculation test (normal equals a negative to one-plus reaction) may be extended to include infants and children of all age levels.

TABLE VII. CASES SHOWING FALSE POSITIVE REACTIONS

Newborn infant	2	
Convalescent influenzal meningitis	2	
Hydrocephalus	1	
Convalescent poliomyelitis	1	
Rheumatic fever, subacute	1	
Birth injury	1	
Postoperative cases	4	
Herniorrhaphy		1
Fracture-dislocation of elbow		1
Tumor of hand, nonmalignant		1
Tendon transplant		1
(Tests done within seventy-two hours of anesthesia)		

CONCLUSIONS

A microtechnique for the cephalin-cholesterol flocculation test utilizing capillary blood is presented in detail.

One hundred eleven parallel determinations revealed 94.5 per cent agreement of the microtechnique with the standard Hanger technique; the microtechnique appeared more sensitive.

Analysis of 284 determinations on pediatric patients with no evidence of liver disease revealed 97.6 per cent of the Hanger reactions and 94.0 per cent of the micro reactions to be one plus or less.

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A METHOD FOR THE DETERMINATION OF NITRATES IN MILK AND INFANT FORMULA

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COMLY,[1] in his report on two case histories of infants having methemoglobinemia, gives a very interesting and thorough history of this problem of high nitrate well water and how it affects the hemoglobin of the blood to cause methemoglobinemia. Comly stated that in trying to analyze the milk formula for its nitrate content, carmelization occurred which prevented completion of the analysis.

The phenoldisulfonic acid method[2] is the usual method of analysis for nitrates; however, in searching through the literature, the method of Noll[3] was noted. This method employed the brucine reagent[4] and had the advantages of simplicity, color stability, few interfering ions (except possible organic material), a sensitivity of 0.3 part per million and an accuracy of 0.5 part per million nitrate in the range of nitrate concentrations from 0 to 50 parts per million as NO_3. Noll adapted a Klett-Summerson photoelectric photometer for nitrate analysis. This method was chosen for use in this investigation.

Since caramelization occurs in analysis of infant formula for nitrate content, it was necessary to remove the sugar (milk sugar and the added sugar from formula) before proceeding with the analysis. The action of acid and heat on the sugar present naturally results in the production of a dark discoloration prohibiting further analysis. As a result, the removal of sugar becomes very important and was accomplished by adapting a procedure similar to that used by Barker and Summerson.[5]

STANDARDIZATION AND RESULTS

Using the method of Noll, a standard nitrate curve was outlined using solutions of known nitrate values. From this calibrated curve the data tabulated in Table I were obtained. A Klett-Summerson photoelectric colorimeter and a blue filter with a range of 400 to 465 mμ were employed. A water blank was used to adjust the instrument to zero.

All results in this work are expressed in terms of nitrate nitrogen. A conversion factor of 4.4 was used to change nitrate values to nitrate nitrogen.

When necessary, the original water sample was diluted with distilled water prior to color development.

In order to analyze infant formula or milk samples for nitrate, the sugar was removed in order to prevent caramelization. As stated previously, this was accomplished by the following adaption from the method of Barker and Summerson.

From the Research Laboratories, Pet Milk Company.

To a 50 ml. centrifuge tube the following materials were added in the order listed:

3.5 ml. infant formula (or milk)
3.5 ml. cupric sulfate (20 per cent)
24.0 ml. distilled water
3.5 Gm. calcium hydroxide.

The tube was stoppered, thoroughly shaken, and let stand for thirty minutes. After standing, the tube was centrifuged until a clear, supernatent layer was obtained. If at all turbid, this layer was pipetted off and filtered (Whatman No. 42). Five milliliter portions were placed in 50 ml. beakers and analyzed for nitrate using the brucine reagent. Another 5 ml. sample was run simultaneously as a blank (no brucine added). Failure to remove sufficient sugar to prevent caramelization would be shown by discoloration in the blank.

TABLE I. NITRATE RECOVERIES USING THE BRUCINE REAGENT

NO.	SAMPLE	NITRATE NITROGEN (PPM)		
		ADDED	FOUND	% RECOVERY
1	Distilled water standard	100	100	100
2	Distilled water standard	100	97.7	97.7
3	Distilled water standard	500	500	100
4	Distilled water standard	500	488.6	97.7
5	Regular evaporated milk	0	1.25	---
6	Regular evaporated milk	70	60.2	86.0
7	Infant formula (not sterilized)	70	60.8	86.8
8	Infant formula (sterilized)	70	60.8	86.8
9	Infant formula (sterilized)	70	61.9	88.4
10	Infant formula (sterilized)	350	336.0	96.0

From Table I it is readily seen that better recoveries were obtained from the regular standards than from the milk samples. All of the samples were carried through the sugar-removing procedure. It is difficult to explain the lower recoveries in the milk samples. Dilution of the filtrate (after centrifuging) and precipitation of excess calcium prior to color development was tried without increasing the recovery percentage. However, even with an 87 per cent recovery, it is felt that this method is still of value in that it permits at least a semiquantitative measurement of nitrate. As a result, by employing this procedure for eliminating the effect of sugar, an estimation can be made as to the nitrate content of milk formula suspected of being responsible for methemoglobinemia.

SUMMARY

A semiquantitative method is outlined whereby milk and infant formula can be analyzed for nitrate without interference by caramelization from lactose or the added sugar in the formula.

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A METHOD FOR THE REMOVAL OF NITRATES FROM WATER PRIOR TO USE IN INFANT FORMULA

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INFANT methemoglobinemia due to high nitrate waters is an important problem, especially in certain rural areas. One of the earliest reports of numerous cases of infants having this disease was in 1945 by Comly[1] in Iowa. Ferrant,[2] and Faucett and Miller[3] also reported methemoglobinemia in infants who had ingested milk diluted with well water having a high nitrate content. In 1947, thirty-three cases were reported in Illinois with five fatalities.[4] No doubt many more similar cases that have not been publicized have occurred elsewhere, especially since it is known that high nitrate waters have been found in at least ten of our states and three foreign countries.

The nitrate nitrogen content of the water used in most of these reported cases ranged from 25 to 300 parts per million.[5] In Comly's report considerable bacterial contamination was noted in the water used, as well as a high nitrate content. However, Johnson[6] and his workers found that a high concentration of nitrate nitrogen can occur in water in which no coliform organisms are demonstrable. Weart[7] states that no correlation was found between the presence of large amounts of nitrate and the sanitary quality of the water. As a result, it appears that there is not anything definitely predictable as to bacterial content and high nitrate content of the waters in question.

Since 1945 there has been more and more attention given this particular infant disease. It is generally noted in rural areas where the water supply is from a shallow well which has been dug rather than drilled. To change the water supply is not often convenient due to adverse weather conditions, transportation problems, or the financial status of the family involved. As a result, it would be advantageous for all concerned if the family doctor had a method for removal of, or at least a safe reduction of, the nitrate content of the water. The doctor could demonstrate the effect of the treatment, and thereafter the family could follow his simple instructions in making routine preparations of low nitrate water for use in the infant formula.

It was with this thought in mind that the following experimental work was conducted and the results given in this report.

The preceding report covered the analytical approach on this problem of nitrate removal from well water to be used by infants, either as drinking water or in milk formula.*

EXPERIMENTAL RESULTS

The thought of trying some ion exchange material seemed the most practical approach in trying to reduce the nitrate content of well water. Meyers,

From the Research Laboratories, Pet Milk Company.
*See page 479.

Eastes, and Meyers[8] predicted many unique or special applications of their synthetic resins. The chemical efficiency and capacity for anion removal by these exchange resins in water purification was shown by Meyers and Eastes.[9] Since our problem involved only the anion, NO_3, we obtained quantities of the anion exchange resins, Amberlite IR-4B and IRA-400, for this work.

The method of Bray[10] was used for a rapid, simple estimation of the nitrate content of water. In this test, a pink to reddish color, which is proportional to the amount of nitrate present, develops.

INITIAL TEST FOR NITRATE REMOVAL

One hundred milliliters of a standard solution (100 parts per million nitrate nitrogen) were mixed for ten minutes with 5 Gm. of the IRA-400 resin. After this treatment, a sample of this water indicated removal of nitrates to approximately 10 parts per million (a slight pink color). The untreated control gave a dark brownish-red color showing excessive nitrates present. This simple test indicated that it was possible to reduce the nitrate content to a safe level and stimulated a series of experiments to determine the following: (1) the minimum exposure time needed to remove nitrates; and (2) the minimum amount of resin for maximum removal of nitrates.

A. *Batch Method for Removal of Nitrate.*—

Series I. IRA-400: One hundred milliliters of nitrate nitrogen standard (100 parts per million) were stirred fifteen minutes with different amounts of the resin with the following results:

No. 1 1 Gm. resin, most red color.
No. 2 3 Gm. resin, less color than 1, more than 3.
No. 3 5 Gm. resin, least color (a slight pink).

Series II. IRA-400: One hundred milliliters of the 100 parts per million nitrate nitrogen standard plus 5 Gm. resin were given different stirring times to give the following results:

No. 1	1 minute	All four stirring times gave a similar color (sl. pink), indicating that only a short exposure time is needed to effect removal of nitrate.
No. 2	5 minutes	
No. 3	15 minutes	
No. 4	25 minutes	

A 10 parts per million nitrate nitrogen standard gave a similar pink color as obtained in Series II.

Series III. IRA-400 and IR-4B: One liter of tap water was placed in a 2 liter screw top jar. Tests for nitrate were made after various shaking times. The results shown in Table I.

These results (Table I) indicate that the most economical amount of resin to give the maximum decrease in nitrates is in 30 Gm. per liter of tap water (100 parts per million nitrate nitrogen added) with a minimum shaking time of three minutes. The resin IRA-400 showed a decided advantage over IR-4B in the speed of nitrate adsorption.

This preliminary work is further supported by the results obtained and shown in Table II.

TABLE I. EFFECT OF VARYING RESIN AND EXPOSURE TIME

NO.	SAMPLE	RESIN (GM.)	TIME SHAKEN		
			1 MIN.	3 MIN.	6 MIN.
	Tap water	0	Red	------	------
	Tap water	10 (IRA-400)	Light red	------	------
I	Tap water with 100 ppm nitrate nitrogen	10 (IRA-400)	Brownish red	Brownish red	Brownish red
	Tap water	30 (IRA-400)	Pink	------	------
II	Tap water with 100 ppm nitrate nitrogen	30 (IRA-400)	Lighter than in I	Light red	Light red
	Tap water	30 (IR-4B)	Darker red than in I or II		
III	Tap water with 100 ppm nitrate nitrogen	30 (IR-4B)	Brownish red, similar to I		

TABLE II. EFFECT OF RESIN ON NITRATE CONTENT AS SHOWN BY BRUCINE REAGENT

NO.	SAMPLE	TREATMENT	COLOR READ	NITRATE NITROGEN (PPM)
1	Tap water (1 L.)*	None	160	9.6
2	Tap water (1 L.)	30 Gm. IRA-400 for 3 minutes	127	1.4
3	Tap water (1 L.)* 100 ppm nitrate nitrogen	None	330	106.8
4	Tap water (1 L.)* 100 ppm nitrate nitrogen	30 Gm. IRA-400 for 3 minutes	138	7.9

*A 1-5 dilution of sample made prior to color development.

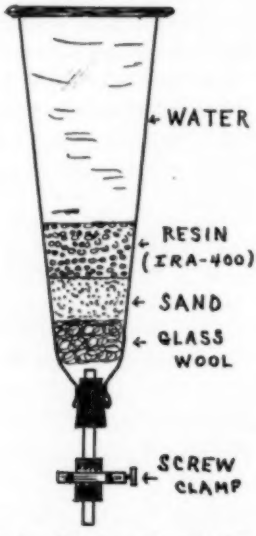

Fig. 1.—Nitrate exchange column.

B. *Exchange Column Removal of Nitrate.*—A very simple ion exchange column was made as shown in Fig. 1. About 22 cubic inches of the anion exchange resin were used to remove the nitrate.

One liter volumes of standard nitrate nitrogen water (100 parts per million) were poured in the top and permitted to stand one minute before draining at such a rate as to make a total exposure time of ten minutes. Five milliliter aliquots of each treated sample were analyzed for residual nitrate by the method of Noll.[11] The above procedure was repeated with fresh untreated portions until the residual nitrate nitrogen approached the safe limit of 10 parts per million nitrate nitrogen.[12]

The results obtained in this experimental column treatment are shown in the respective curves in Fig. 2. Tap water and distilled water were used.

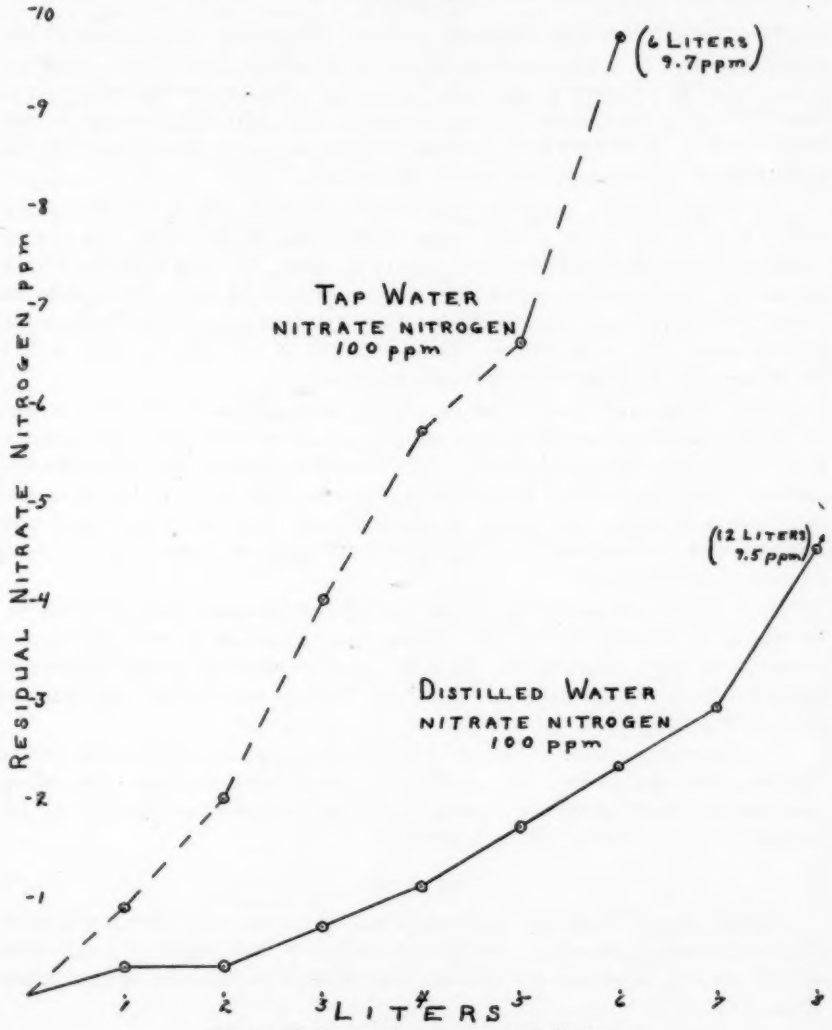

Fig. 2.—Exchange column removal of nitrate.

A new resin bed was prepared for use with each type of water. A maximum of 6 L. tap water (100 parts per million nitrate nitrogen) and 12 L. distilled water (100 parts per million nitrate nitrogen) were treated by this method.

The tap water used in this ion exchange column had a hardness of 34 grains and about 600 parts per million total solids. The effect on pH was followed in the tap water series with little change noted. The tap water had an initial pH of 7.25 and 7.05 for the first liter. A maximum pH of 7.65 was obtained in the fifth liter and a slight decrease in the last (sixth) liter to be treated, pH 7.4.

DISCUSSION

The method of nitrate removal presented is another application of ion exchange which is used so extensively in water purification. The amount of resin needed is not very great; however, a cost estimate for this treatment is uncertain at this time, since production of this resin (IRA-400) is being shifted from research to industrial quantities.[13] The increased production should make this simple treatment even more economical.

The batch method would be the easiest and most simple for the family doctor to demonstrate in a rural area. The doctor could supply the needed resin and make the initial tests for nitrate removal. A large fruit jar with a screw top would suffice as the agitating container. A clean cloth (cheese cloth) tied or held over the jar top would retain the resin while pouring the treated water into a container. Small volumes of low nitrate water could be prepared quickly by this very simple treatment.

The column method, once set up, would, perhaps, be the most convenient and economical for preparing large volumes of low nitrate well water directly in a rural area. The exact volume which could be treated will vary with the different characteristics of the water in question. The effect of hardness and total solids in water was shown by the different volumes of tap water and distilled water which could be treated, even though each contained the same amount of added nitrate.

It would be advantageous to use a simple confirmatory test (Bray's) for the degree of nitrates present prior to treatment or actual usage of the treated water in formula preparation. In order to avoid having sodium hydroxide around infants or infant food preparations, it would not be suggested that one attempt regeneration of the material.

It is important to note that this resin treatment, while reducing the nitrate content, does not reduce any possible bacterial contamination. Therefore, the treated water should be given the heat treatment as directed in the preparation of the respective milk formula.

SUMMARY

Experimental work was conducted and data presented showing it practical and possible to reduce the nitrate content of well water to a safe level by the use of a rapid anion exchange resin either in a batch or column operation.

The author wishes to thank the officials of the Pet Milk Company, especially Dr. E. A. Louder, Technical Director, for releasing this report for publication, as well as for his supervision of the research program. The author also wishes to thank Dr. A. Z. Hodson for his advice and criticism during the course of this work and in the preparation of this paper.

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Case Reports

SUBLINGUAL HEMATOMA AS AN UNUSUAL COMPLICATION OF HEMOPHILIA

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THIS unusual complication of hemophilia, sublingual hematoma, occurred in a Brazilian boy 10 years of age. He is the oldest of four children. His younger brother, aged 5 years, is also a known hemophiliac and another boy who was born between the patient and his younger brother died at the age of 14 months of hemorrhage ascribed to hemophilia. The fourth child, recently born, was a female. One brother of the mother died during early childhood of hemorrhage presumably due to hemophilia. The father of the patient, a very intelligent young officer in the Brazilian Air Force, had made a very intensive study of the maternal family tree. He was able to uncover only two other hemophiliacs, the maternal uncle mentioned above, and a maternal cousin. The family tree is shown in Fig. 1.

CASE HISTORY

This 10-year-old white boy, a known hemophiliac, entered Children's Hospital on October 31 with a chief complaint of nausea and vomiting dating back to five days before hospital entry.

At onset, the vomiting was not severe but persistent. The following day the vomiting subsided and reappeared the next day. On this day there was an elevation of the temperature to 100.6° F. and mild abdominal discomfort. The patient continued in this status until the morning of his hospital entry when there was a rather marked abdominal pain and his private physician found rigidity over the right lower quadrant and some fullness in the pelvis upon rectal examination.

In discussing the history with the child, it was brought out that on the day of the onset he had fallen over another boy's foot and in so doing had struck his abdomen in the region of the symphysis. There was no history of immediate pain following the fall. No history was obtained of urinary symptoms during the duration of the present illness. Bowel habits were not unusual and there was no history of bloody or tarry stools.

The family history has been elaborated above. The past history revealed that the child had had numerous episodes of bleeding from minor traumata, all of which had necessitated repeated blood transfusions. He also had had numerous episodes of hemarthrosis which have resulted in considerable deformity and a peculiar "waddling" gait.

Physical examination revealed a thin white boy of stated age who lay in bed on his side with his knees drawn up. The child did not appear to be in any great pain. His face was "pinched" and "drawn" and there were deep circles under both eyes.

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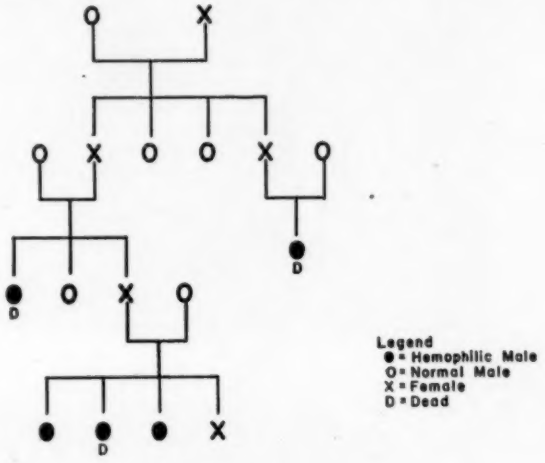
The remainder of the physical findings were confined to the abdomen and rectum. The abdomen was scapoidlike and moved well with respiration. There was no pain to deep palpation anywhere over the abdomen and there was no rebound tenderness. Peristalsis was normal.

The examining finger was introduced through the anal sphincter with ease. Muscle tonus was good. The prostate was not felt. There was no definite mass; however, there was a definite fullness in the pelvis anteriorly. The boy had voided approximately fifteen minutes before examination; therefore, this was not considered to represent a urine-filled bladder. The remainder of the pelvis was normal. The rectal examination was accompanied by only a moderate amount of discomfort.



Family Tree Of C. J.

Fig. 1.

A hemogram performed on entry showed 13 Gm. of hemoglobin, 5 million red blood cells, and 14,100 leucocytes with 79 per cent neutrophiles. Of the latter, 9 per cent were band forms. A urinalysis was normal. The following day the white blood count was 16,100 with 62 per cent neutrophiles. Subsequent leucocyte counts were all within normal limits as to total numbers and percentages of the component cells.

The patient was seen in surgical consultation about an hour after the initial hospital examination. At that time there was no evidence of abdominal tenderness or rigidity. Upon rectal examination the consultant was able by bimanual palpation to reach the anterior abdominal wall with the rectal finger.

Hospital Course.—The evening of hospital entry the boy complained that his tongue felt thick. Inspection of the tongue at that time did not reveal any abnormality of lingual or sublingual tissue nor of the overlying mucous membranes.

The following morning there was present beneath the tongue a large hematoma which appeared to be larger on the right side. The hematoma did not seem to be in the substance of the tongue, but rather in the sublingual loose connective tissue.

An immediate attempt was made to secure some Fraction I anti-hemophilic globulin. Since none of this was available, upon the advice of Dr. C. A. Janeway, a transfusion of 200 c.c. of compatible blood was given within an hour after it was drawn.

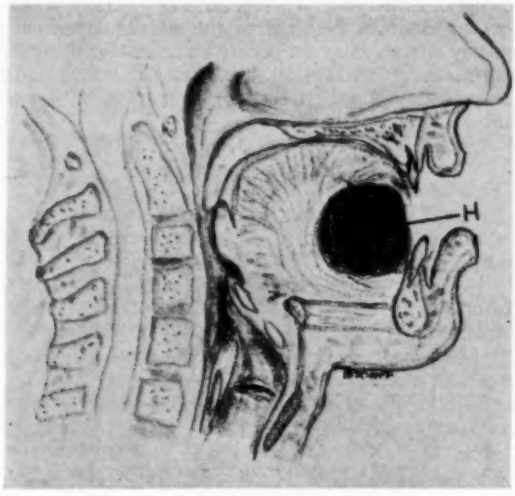


Fig. 2.

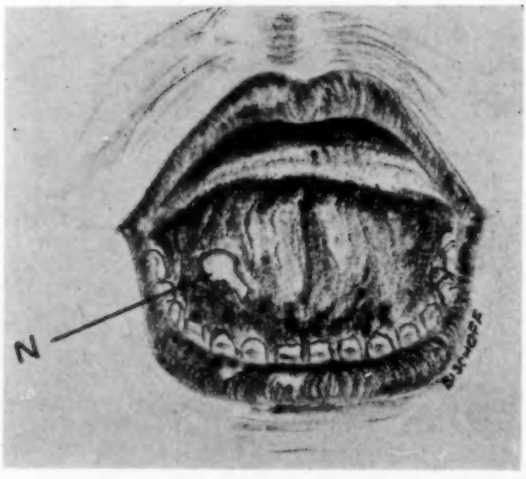


Fig. 3.

In the afternoon of the day that the hematoma appeared, it appeared larger than it did in the morning. Whereas in the morning the hematoma seemed to be limited more to the right side, in the evening it was, along with being larger,

symmetrically distributed on the two sides. By evening the boy's speech was very thick and quite difficult to understand. At this point when the child's mouth was opened the dorsum of the tongue approximated the roof of the mouth.

The following morning another transfusion of 100 c.c. of less than one-hour-old blood was given. In the afternoon of this day there seemed to be some space between the dorsum of the tongue and the hard palate. There also appeared to be more space on the left side. Inasmuch as the tongue had come down some, it was presumed that the bleeding had stopped.

The next day there was an unmistakable odor of old blood about the boy's breath. The mucous membrane of the underside of the tongue contained some areas on the right side which appeared to be becoming necrotic. The saliva which collected on the side of the mouth during examination was stained with blood. The papillae of the lateral margins of the tongue stood out in "bas relief" and the edges of the tongue had the appearance of a tissue undergoing necrobiosis. One-half strength Dobell's solution as a mouth wash and penicillin troches were prescribed at this time for their local effect.

By the next evening the tongue had almost regained its normal shape and size. It was heavily coated over its posterior portion while the anterior portion was a deep purple in color. In spite of the rather cadaverous appearance, the tongue was still freely movable. The hematoma, still present, was quite small. At this point the temperature which had previously been within normal limits, elevated to 102° F. rectally. It was thought at this point that the temperature elevation represented an infection of the hematoma and early abscess formation. Sulfadiazine, one and one-half grains per pound, was started immediately.

On the morning of his sixth hospital day, the day following the temperature elevation, the left faucial tonsil, previously normal, was enlarged and contained a number of yellow, follicular areas. This apparently explained the temperature elevation.

The child was discharged on his eighth hospital day. Upon discharge from the hospital, the tongue was of normal size. There was a minimum of discoloration over the inferior, anterolateral surface of the tongue. The mucous membrane of the sublingual area appeared to be well healed. The child's voice was again clear and comprehensible both in his native language and in English.

DISCUSSION

Since 1910 there have been eight case reports in the literature of sublingual hematoma as a complication of hemophilia.[2-9] Of these eight cases, four had tracheotomies and of these four, only one survived. In the case presented at no time was there respiratory embarrassment or complete inhibition of swallowing. Although tracheotomy was at all times kept in mind as a possible eventuality, it was not necessary to resort to this procedure. Because of the fact that this child never did have difficulty with either respiration or deglutition, it was considered that the hemorrhage did not involve the muscular tissue of the tongue or the floor of the mouth. Fig. 2 shows the most probable location of the hematoma in the submucosal tissue of the sublingual area. Fig. 3 is a drawing reproducing a frontal view of the hematoma. The small area labeled "N" shows the area of necrosis.

It has been shown that the antihemophilic activity of both blood and plasma gradually disappears even though it is preserved at refrigeration temperatures.[10] Accordingly, the child was given transfusions of blood within one hour of the time that it had been drawn. In this connection, it is interesting to note that both the patient and his younger brother had had episodes of bleeding a few years before which had not responded to transfusions of citrate blood, but which had responded immediately to direct blood transfusions.

SUMMARY

A case of sublingual hematoma as a complication of prolonged vomiting in a hemophiliac is presented. This increases the total number of this complication to nine since 1910.

The bleeding was controlled through the use of compatible blood administered within an hour after it had been drawn.

A brief summary of the literature is presented.

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ACUTE INFECTIOUS LYMPHOCYTOSIS

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INTRODUCTION

ACUTE infectious lymphocytosis is a specific disease process which is both infectious and contagious. The most characteristic feature of this disease entity is a benign hyperleucocytosis due to a relative and absolute increase of the small lymphocytes. The morphology of these lymphocytes is normal in all respects and the leucocytosis persists for approximately two to seven weeks.[7-9] The clinical symptoms are generally mild, but in certain instances they have been severe enough to warrant active medical care and hospitalization.[2] Of particular interest is the general paucity of physical findings, particularly the absence of lymphadenopathy and splenomegaly. The Paul-Bunnel test is regularly negative.

In 1941 Reyersbach and Lenert[6] reported from a children's convalescent rheumatic home sixteen cases of asymptomatic hyperleucocytosis with a predominating lymphocytosis. Although the abnormal cell type typical for infectious mononucleosis was absent and the Paul-Bunnel test was negative in all cases, they regarded this outbreak as an aberrant form of infectious mononucleosis. To substantiate their contention, they cited a case reported by Wilson and Cunningham[11] as an instance of infectious mononucleosis without signs or symptoms. This latter case was identical to the series of Reyersbach and Lenert in all respects, but no heterophile test had been done. The first complete description of this disease entity was presented by Smith.[7] In a two-case report the author laid down the principles for this disease and its differential diagnosis. At this time Smith established the disease as a separate entity and designated it as acute infectious lymphocytosis.

Duncan[1] was the first to report a case of acute infectious lymphocytosis associated with symptoms and physical signs. At the onset abdominal complaints and findings were evident and during the first week suggestive neurological involvement was observed. The abdominal complaints were fleeting in nature and were attributed to a hyperplasia of the mesenteric lymph nodes, while the neurologic changes and the accompanying fever were regarded as part of a generalized illness.

In 1944 Smith[8] reported four additional cases of acute infectious lymphocytosis. The communicability and the infectious nature of this disease was demonstrated. At this time the author discussed in greater detail the various aspects of the illness and presented further confirmatory evidence that the disease constituted a specific entity and could readily be separated from associated syndromes and blood disorders.

Since the classic papers by Smith,[7, 8] a number of additional cases have appeared in literature.[2-4, 12] The majority of the cases have been observed in children, although in three instances young adults have shown evidence of acute infectious lymphocytosis.[2, 4] A most complete survey of this disease is included in a recent monograph.[9]

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CASE REPORT

K. B., a 5-year-old Negro female, was admitted to a hospital on July 18, 1946, with the chief complaint of pain in the abdomen and knees of three days' duration. The physical examination revealed a slight cardiac enlargement, a blowing apical systolic murmur, and a temperature 102.4° F. The x-ray on admission was interpreted as showing a pneumonic infiltration in the right upper lung field. The infiltration persisted and when a positive Mantoux was discovered the diagnosis of pulmonary tuberculosis was established. The patient was transferred to the Pediatric Division of Sea View Hospital on Oct. 3, 1946.

The past history was entirely negative. Birth and developmental course were not remarkable. The mother states that the child had been entirely well until July, 1946, at which time the fever was first noted. No additional history could be obtained.

The only notable finding on admission to Sea View Hospital was a small umbilical hernia. The other findings were within normal limits. The admission laboratory studies revealed a normal urine; feces and gastric specimens were negative for acid-fast bacilli; sedimentation rate was 11 mm. per hour; blood sugar was 95 mg. per cent and urea nitrogen 11 mg. per cent; Wassermann test was negative; red blood cells were 3.82, hemoglobin 10 Gm. or 69 per cent; white blood cells 9,700, polymorphonuclears 41, lymphocytes 56, monocytes 1, nonsegmented polymorphonuclears 2, eosinophiles 0; Schick test was positive; and Mantoux was positive (1:1,000,000). The admission x-ray of the chest was interpreted as revealing a small nodular focus of infiltration in the mesial portion of the upper lobe of the right lung. No evidence of cavitation or consolidation was seen, nor was there any enlargement of the mediastinum or paratracheal nodes.

Course.—The patient's hospital course was very mild save for a few intercurrent infections and one episode of phlyctenular conjunctivitis. In July, 1947, a dermatitis of the scalp was noted. These lesions revealed a greenish fluorescence under the Wood's light and the diagnosis of tinea capitis was made. The lesions persisted despite vigorous therapy, and in January, 1948, they were observed to be secondarily infected with resultant postauricular adenopathy. The child was placed on a regime of scalp scrubs with tincture of green soap twice daily. The skin lesions responded well and were soon healed with a concomitant reduction in the size of the lymph nodes draining this area.

Throughout her course the patient had been afebrile and had shown a progressive weight gain. Monthly gastric aspirations were all negative for acid-fast bacilli, and the chest, viewed roentgenologically, revealed a resolution of the pulmonary lesion. In view of these findings the child was re-evaluated for discharge in February, 1948. A blood count taken on Feb. 9, 1948, showed a red blood cell count of 4.57; hemoglobin 12 Gm. or 83 per cent; white blood cells 64,750, with segmented polymorphonuclears 9, eosinophiles 5, lymphocytes 87, basophiles 0, nonsegmented polymorphonuclears 0, monocytes 0. A repeat blood count on the following day revealed 60,400 white blood cells, polymorphonuclears 14, lymphocytes 85, monocytes 1, nonsegmented polymorphonuclears 0, eosinophiles 0, and basophiles 0. A sternal marrow smear taken at this time revealed a predominance of the small mature lymphocytic forms. (See Table II.)

Daily physical examinations were carried out in order to determine the etiology of the elevated white blood cell count. These examinations were all negative. The child's temperature remained normal. A review of the patient's course revealed no illness or temperature elevations during the two

TABLE I. K. B. BLOOD COUNTS PRIOR TO, DURING, AND AFTER ACUTE INFECTIOUS LYMPHOCYTOSIS

DATE	R.B.C.	HGB. (%)	HGB. (GM.)	W.B.C.	POLY-MORPHO-CLEARS	LYMPHO-CYTES	MONO-CYTES	NONSEG-MENTED POLY-MORPHO-NUCLEARS	EOSINO-PHILES	BASO-PHILES
10/17/46	3.82	69	10	9,700	41	56	1	2	0	0
1/17/47	3.29	69	10	11,050	55	40	3	1	2	0
10/21/47	3.23	62	9	10,900	73	19	6	2	0	0
2/ 9/48	4.57	83	12	64,750	9	89	0	0	5	0
2/10/48	—	—	—	60,400	14	85	1	0	0	0
2/16/48	—	—	—	59,700	21	73	0	2	4	0
2/25/48	4.01	86	12.5	10,400	23	68	1	1	7	0
2/27/48	—	—	—	10,350	31	62	3	1	3	0
3/ 2/48	3.56	72	10.5	9,750	51	38	7	2	3	0
3/ 5/48	—	—	—	11,750	51	41	0	1	7	0
3/12/48	—	—	—	11,400	46	44	1	2	7	0
3/19/48	—	—	—	9,400	32	58	0	2	8	0
4/ 7/48	3.56	69	10	10,600	57	35	0	1	7	0
6/18/48	—	—	—	8,700	50	44	2	1	3	0
6/30/48	3.80	76	11	6,800	37	55	1	0	6	1

Discharged July 1948.

months preceding the leucocytosis. Serial roentgenograms failed to demonstrate an exacerbation of the healing tuberculous lesion. The child was closely observed for isolated episodes or paroxysms of coughing, but the clinical picture was entirely negative for pertussis. Nose and throat cultures, as well as a cough plate on special media failed to reveal any Hemophilus organisms. Further studies on the patient disclosed an erythrocyte sedimentation rate of 13 mm. per hour; bleeding time two minutes; clotting time 2.5 minutes, and repeated urines were essentially negative. Blood drawn for a heterophile serologic study was reported as negative. After Feb. 10, 1948, there was a gradual reduction of the total leucocyte and lymphocyte count until normal levels were reached on Feb. 25, 1948. A sternal marrow smear taken on March 5, 1948, was interpreted as being entirely normal. (See Table II.) All blood smears were closely studied, but in no instance were the large abnormal mononuclear cells characteristic of infectious mononucleosis seen.

TABLE II. K. B.: STERNAL MARROW CELL COUNTS*

CELL TYPES	FEB. 13, 1948	MARCH 5, 1948
Polymorphonuclears, nonsegmented	11.5	20
Polymorphonuclears, segmented	1.5	24
Neutrophilic myelocytes	15.5	15
Eosinophilic myelocytes	7	5
Metamyelocytes	2	2
Normoblasts	12	5
Small lymphocytes	50.5	29
Total	100.0	100.0

*These figures represent the frequency of occurrence per 100 cells counted.

In the four-month period following the discovery of this abnormal blood count the child remained entirely well and was subsequently discharged from the hospital. The diagnoses considered during the illness included infectious mononucleosis, acute infectious lymphocytosis, acute and chronic lymphatic leucemia, pertussis, an exacerbation of the tuberculous process, and an aberrant stimulation of the bone marrow as a result of the intermittent exposure to the Wood's light rays.

DIFFERENTIAL DIAGNOSIS

At the time the elevated white blood count was discovered, the main problem was one of differential dignosis. A complete review of the child's course for the preceding two-month period and the entirely negative physical examinations helped to rule out the intercurrent and contagious diseases of childhood. Because of negative tests for heterophile antibodies and in the absence of typical blood findings, lymphadenopathy, and splenomegaly, infectious mononucleosis was eliminated as a possible diagnosis. Pertussis was unlikely because of the negative cough plate and negative nose and throat cultures for the Hemophilus organisms, as well as the total absence of the characteristic paroxysmal cough. Acute lymphoblastic leucemia was regarded as unlikely because the characteristically large, immature forms were absent in the peripheral blood and bone marrow smears. The uniformity and size of the lymphocytic cells, as well as the subsequently normal blood counts was unequivocal evidence against this fatal blood disease. Chronic lymphatic leucemia more closely resembles acute infectious lymphocytosis in cell morphology. However, this blood disorder was unlikely because of the absence of the usual clinical findings (lymphadenopathy, splenomegaly, anemia, and thrombocytopenia), and the return of a normal blood picture.[8, 9]

It is a well-known fact that lymphocytosis is commonly seen in cases of tuberculosis and a combination of leucocytosis with lymphocytosis accompanies the spread of this infection. However, in this patient the clinical picture was normal throughout, and the laboratory studies and x-rays of the various organ systems showed no exacerbation or further tubercuious involvement.

Another factor in the differential diagnosis was the physical or chemical stimulation of the bone marrow by repeated exposure to the Wood's lamp. A careful review of the literature failed to reveal any previous reports of this type of blood picture response. However, it is well known that the marrow system may respond to diverse physical and chemical stimuli. Prior to the hyperleucocytosis, discovered in Feb., 1948, the child had been observed under the Wood's light two or three times a week. Each exposure lasted approximately 30 to 45 seconds, and in no instance was it prolonged over one minute. Because of the possible etiological affect of this physical ray, the child was no longer observed under the Wood's lamp. By Feb. 25, 1948, the blood picture was normal again. In order to test the hypothesis, the child was exposed daily to the Wood's rays for a two-minute period. This procedure was performed for a ten-day period. During this interval the peripheral blood remained within normal limits. On the eleventh day of exposure a sternal marrow smear was interpreted as being entirely normal. (See Table II.) Thereafter, the child was exposed to these rays three times weekly for two-minute periods. No further abnormalities were observed.

Another physical stimulus to which the patient had been exposed was the radiation of the x-ray machine. This influence can readily be discarded because of the relatively long intervals (three months) between exposures and the failure to observe further hemic abnormalities during subsequent radiation.

The final diagnosis was acute infectious lymphocytosis. Not only were the diseases considered in the differential diagnosis refuted by the clinical and laboratory data, but the observations made in this case coincided with the criteria set up for acute infectious lymphocytosis.

COMMENT

In the few years that have elapsed since Smith's recognition of this syndrome,[7] about fifty cases have appeared in the literature.[9] Of these, twenty-

one cases observed by Finucane and Phillips[3] were on the wards of a tuberculosis sanitorium. Martens[5] has recently reported an additional twenty-two cases of acute infectious lymphocytosis from a Swiss hospital for tuberculous children. Whether or not tuberculous patients have a predisposition to developing acute infectious lymphocytosis will become the subject of a subsequent report.

Another remarkable feature of this case was the height (maximum of 64,750 leucocytes per cubic centimeter) to which the blood count rose. Smith[9] and others have stated that the highest incidence of this disease is in children from one to 14 years of age. Smith places the peak within the first ten years of life. To date, only three cases have been reported outside of this age range, all of whom were within the third decade of life.[2, 12] Close scrutiny of the published cases reveals an inverse relationship between the age of the patient and the height of the leucocyte count. The highest counts were generally observed in the youngest patients. This phenomenon was observed in our patient and lends further strength to this concept.

In previous reports, Finucane and Phillips,[3] Smith,[9] and Isreals[4] have noted an increase in the eosinophilic leucocytes during the course of the disease. Finucane and Phillips state that the eosinophilia occurs at the peak of the white blood count, or shortly thereafter. The duration of the eosinophilia has been variable. In the case reported by Isreals the number of eosinophiles returned to a more normal level with the resumption of normal leucocyte counts. Finucane and Phillips observed eosinophilia for a seven-month period. In the reported case an increase in the eosinophilic leucocytes was noted throughout the more acute phases, and persisted for over five months to the time of discharge.

SUMMARY

1. A brief review of the origin and establishment of this disease entity is presented.

2. A case closely followed is presented to augment approximately fifty cases appearing in the literature.

3. The etiological significance of various physical agents, e.g., the Wood's light, are considered in detail.

4. The possible relationship and frequent occurrence of acute infectious lymphocytosis in tuberculous individuals is noted.

5. Mention is made of a persisting eosinophilia following the return to more normal leucocytic counts.

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SERIOUS TOXIC REACTION ASSOCIATED WITH ADMINISTRATION OF BAL

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BAL has been widely used in the treatment of heavy metal poisoning. Recently Warkany and Hubbard,[1] Bivings and Lewis,[2] and Elmore[3] have reported its use in acrodynia. None of these reports has mentioned a "shocklike" state as occurring during BAL administration.

The following case, illustrating the occurrence of repeated peripheral vascular collapse in a patient receiving BAL, seemed sufficiently important to warrant reporting.

CASE REPORT

F. H., a 15-month-old white female infant, was admitted to the Pediatric Service of the North Carolina Baptist Hospital Oct. 4, 1948, with the complaint that during the previous month the child had "lost her appetite, had lost 6½ pounds of weight, had stopped walking and talking, and had developed a red rash on her feet and hands."

She had been perfectly well until one month prior to entry, when she developed anorexia, became irritable, and developed oliguria. She had no fever. The family physician found "pus" in her urine and gave her sulfadiazine for two days. After this she became weak, the anorexia increased, and she stopped walking and talking.

One week before admission her palms and soles became bright red, and an erythematous rash spread over her lower extremities, abdomen, and back. She rubbed her palms and soles constantly, assumed bizarre positions, perspired freely, and cried out when handled.

Past History.—She had four or five episodes of cyanosis during her second week of life, but otherwise had been well and developed normally. A history of contact with mercury could not be elicited. She had not had teething powders, calomel, treatment for "worms," nor local applications containing mercury.

Physical Examination.—On admission her temperature was 98.6° F. rectally; pulse was 120 per minute; respirations, 24 per minute; and blood pressure, 144 systolic and 104 diastolic. General examination revealed a miserable, poorly nourished female infant with bright red, peeling palms and soles, and an erythematous, macular rash on her lower extremities, abdomen, and sacral region. Respiration was increased, and marked hypotonia was present. Two lower incisor teeth were loose. She had no photophobia nor alopecia. There was no question about the diagnosis of acrodynia.

Laboratory Findings.—Urinalysis was negative; hemoglobin, 13.5 Gm. per 100 c.c.; red blood count, 4.53 million per cubic millimeter; white blood count, 11,500 per cubic millimeter with a differential of 46 per cent segmented polymorphonuclear neutrophiles; 2 per cent nonsegmented polymorphonuclear neutrophiles; 48 per cent lymphocytes; and 4 per cent monocytes. Blood Kahn was negative. Stool examination was negative for blood, ova, and parasites.

Progress.—The first week in the hospital the patient received supportive therapy, and her general condition was unchanged. Her blood pressure re-

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mained elevated and she slept only one-half to two hours a day. She developed conjunctivitis.

On October 12, eight days after admission, she developed physical and x-ray findings of pneumonitis in both lower lung fields. She was given 300,000 units of Duracillin daily. Although her temperature returned to normal in three days, her general condition became worse. Four loose teeth fell out of her mouth. Anorexia became so severe that gavage feedings were necessary.

One hundred cubic centimeters of urine* obtained in a mercury-free container on October 10 were found to contain 370 μg of mercury per liter. This was considered a "very large" amount.

On October 18, fourteen days after admission, she was started on intramuscular BAL 10 per cent with benzyl benzoate 20 per cent in peanut oil. The dosage schedule used by Elmore[3] was started. This schedule consists of giving intramuscular BAL 2.5 mg. per kilogram and 0.5 c.c. of 2 per cent procaine every four hours for twelve hours, then every six hours for forty-eight hours, and then every twelve hours for eight additional days.

On October 19, after seven doses of BAL with procaine, she became very listless, vomited several times, had increased salivation, had six foul, watery, greenish-yellow stools, and her temperature became elevated. The next morning, two hours after the tenth dose of BAL, her temperature was 102.4° F. rectally and she appeared to be in shock with cold, clammy extremities, and had a feeble heart action with a rate of 200. The radial pulse was not palpable, and the blood pressure could not be obtained. Blood studies at that time revealed a carbon-dioxide combining power of 16.7 meq. per liter (37 volumes per cent) and chlorides of 91.5 meq. per liter (536 mg. per cent). Her hemoglobin was 11 Gm. per 100 c.c. and white blood count 26,800 per cubic millimeter. Plasma, 5 per cent glucose in distilled water, and whole blood were given intravenously, and the peripheral circulation improved. Her temperature rose to 106° F. rectally, but returned to normal within sixteen hours. Blood culture was negative. She was again put on prophylactic doses of penicillin.

During the next four days she seemed to improve generally. The erythema of the palms and soles decreased, and she took her feedings better.

On October 24 the patient was given one test dose of 17.5 mg. of BAL and 0.5 c.c. of procaine intramuscularly without reaction. This was repeated on October 25 without reaction. On October 26 the original dosage schedule as previously described was resumed.

On November 2, after seventeen injections of BAL, she became listless, vomited, and developed diarrhea. Blood studies at that time revealed a carbon-dioxide combining power of 15.8 meq. per liter (35 volumes per cent), hemoglobin of 15 Gm. per 100 c.c. of blood, and white blood count of 18,850 per cubic millimeter. BAL was stopped, and twelve hours later she presented a picture of shock identical with the first episode except that her temperature rose only to 104.2° F. rectally. She again recovered after the intravenous administration of plasma, normal saline, and 5 per cent glucose in distilled water. On November 3, sixteen days after institution of BAL therapy, her urine contained 100 μg of mercury per liter.

She developed two episodes of pulmonary congestion manifested by numerous moist râles scattered throughout the lung fields, following vigorous and rapid administration of intravenous fluids. The remainder of her hospital course was uneventful. She was discharged on November 23, improved.

On December 7 she was seen in the Outpatient Department and improvement had continued.

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*The mercury determinations on the urines were done by Dr. Josef Warkany and Mr. Donald Hubbard of the Children's Hospital Research Foundation, Cincinnati, Ohio.

COMMENT

This case demonstrated the occurrence of a "shocklike" state in a patient receiving BAL. A definite association between BAL administration and the clinical picture of shock in this patient was not established. Procaine or the preservative benzyl benzoate may have contributed to this infant's reaction. Although the mechanism of collapse in this patient was not definitely determined, certain possibilities were considered. The effect of BAL on the autonomic nervous system with a vasomotor response resulting in peripheral collapse could explain the shocklike picture in the patient. The relationship between the blood volume and urine output and fluid intake has also been considered as an explanation for the peripheral collapse. The function of the adrenal cortex could also be affected by BAL and result in this type of peripheral vascular collapse.

SUMMARY

A case is reported of an infant who developed peripheral vascular collapse on two occasions while receiving BAL. Although BAL may prove to be a beneficial agent in the treatment of acrodynia, this case report suggested the possibility that BAL may cause serious toxic reactions in some patients.

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Clinical Conference

CONFERENCE AT THE UNIVERSITY OF ARKANSAS HOSPITAL*

WILLIAM A. REILLY, PROFESSOR AND HEAD OF PEDIATRICS

Case 1. Typhus Fever

DR. A. KRIEGER (Intern).—J. L. (private patient of Dr. Sam Phillips, Baptist Hospital), a male infant, aged 16 months, was taken ill Dec. 17, 1948, with listlessness and slight fever; two days later a petechial rash came out on the feet, legs, forearms, hands, and face, and gradually spread over the rest of the body; on the eighth day swelling began on the ankles and spread over the body. His fever rose soon after onset to 102 to 104° F., which it was at admission on Dec. 26, 1948. He had been playing with wild animals, made pets. There were numerous rats in his home.

The family and past history did not reveal any significant facts.

On admission on the ninth disease day he appeared well developed and nourished, lying quietly but somewhat stuporous. There was generalized mild edema. Petechial hemorrhages were seen in the skin over all the body and in the mucosa of the mouth; the throat was injected. There were no meningeal signs, adenopathy, or hepatosplenomegaly. The remainder of the physical examination was not remarkable.

The clinical impression was that he had typhus fever.

Laboratory Findings.—Repeated urinalysis showed occasional traces of albumin and rare casts. There was moderate hypochromic anemia with hemoglobin of 75 to 55 per cent and 3.95 to 3.2 million red blood cells. The white blood cells ranged between 17,500 to 22,000 with 70 to 84 per cent neutrophils during the first hospital week to 13,000 to 15,000 with 55 to 65 per cent neutrophils during the last week in the hospital when fever was slowly disappearing (twenty-sixth to thirty-third day of disease). The Weil-Felix blood agglutination with *Proteus OX19* was positive on the tenth disease day at the 1-400 dilution and on the thirteenth day the positive dilution had increased to the 1-800 dilution. A blood culture on admission was still negative after fourteen days. Agglutinin tests for typhoid, paratyphoid, and undulant fever organisms were negative on admission.

Course and Treatment.—The boy remained acutely ill and stuporous, had muscular twitching, some right-sided spasticity, strabismus, and irregular, rapid respiration. A new rash came out and he had to be tube fed during the first hospital week (ninth to sixteenth disease days). The rash disappeared by the twentieth day. In general, he improved markedly after that time but there was some residual spasticity and nervousness. Fever came down gradually over a course of twenty-eight days from onset of first symptoms. There was a mild diarrhea from the seventeenth to nineteenth disease days.

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Penicillin was given during the first two hospital days. Sulfadiazine (2.0 Gm. daily) was given from the twelfth to eighteenth hospital days. Aureomycin (Duomycine of Lederle Laboratories) was started on the eleventh disease day by stomach tube, 750 mg. for the first dose and 250 mg. every four hours for two doses; then 60 mg. of it were given intramuscularly every four hours for the next seven days (until the eighteenth day). There was sudden and marked improvement soon after starting aureomycin, for he changed from a critical state to one with less stupor and twitchings; devervescence started then. Two supportive transfusions were given on the twelfth and fourteenth disease days.

When last seen, eight weeks after onset, all spasticity, inability to focus his eyes, nervousness, etc., had disappeared.

DR. PHILLIPS (Associate Professor of Pediatrics).—Typhus or meningococcus were considered the most likely causes. The latter did not seem to be the cause, because when I first saw him on the ninth disease day as yet there were no meningeal signs, the rash was more petechial than purpuric. It is true that later he developed strabismus and right-sided spasticity. Yet in the meantime he had been on doses of sulfadiazine adequate to control such a meningitis and had some penicillin. A blood culture, too, was negative. The points in favor of typhus fever were: the onset with fever and listlessness and the appearance of the rash on the second day. The rash at onset may have been pinkish-red, as in typhus macules; on entry it was petechial and widespread, as in typhus fever. It started on the limbs as in Rocky Mountain fever.

The profound stupor, critical condition, the injected conjuctivae and coated tongue are characteristic of typhus. When the Weil-Felix reaction was so strong and became more so three days later, we were certain of typhus as the cause. The presence of rats and wild animal pets were other helpful points; no other cases have occurred in the area. No louse or flea bites were found on the child.

Dr. William A. Reilly suggested the use of aureomycin. The boy was profoundly ill and improved rapidly and greatly when aureomycin was given. His fever, which had been on a plateau for some days, gradually came down during the time aureomycin was given (seven days). Sulfadiazine was used during the same time; it may be that another infectious agent was complicating the picture and that continued usage of sulfadiazine might have stopped fever sooner, for it continued for seven days after both drugs were stopped. It is thought that typhus fever is stopped in several days by aureomycin and that only five to seven days' therapy with it is all that is needed.

DR. REILLY.—This boy had a clinical picture of typhus very similiar to the great numbers I had seen in French Morocco. The fever was a bit long, twenty-eight days, for endemic typhus which we have in Arkansas, but I think that he likely may have had a complication with another organism. It was not possible to do a guinea pig inoculation or blood tests for rickettsial agglutinations, neutralizing antibodies, or complement fixation for differentiation of rickettseae.

Typhus in Arkansas is diminishing yearly; the median number of cases between 1943-47 was nineteen yearly.

It is the endemic type, *Rickettsia mooseri,* which is rat-borne by the flea to the human; there is a mortality of about 2 per cent over the country; it is more common in winter, whereas Rocky Mountain fever occurs in the early spring and summer and has not been seen very often in Arkansas.

There are three "specifics" for rickettsial diseases—para-aminobenzoic acid, chloromycetin, and aureomycin. The first should be given in the first week of disease and is inferior to the other two. Chloromycetin[1] is very effective for the several typhus fevers and Rocky Mountain spotted fevers; it was not available. Aureomycin has been used successfully against Rocky Mountain fever. Smadel and associates[2] have shown this experimentally and clinically. Because of the similarities of the rickettsia of that disease and that of endemic typhus and the availability of aureomycin, we used it. The supply and monies for a purchase limited our use to seven days. The dose was 75 mg. per kilo on the first day. We reduced it thereafter to about 20 mg. per kilo daily. Some typhoid patients have received 300 to 500 mg. per kilo daily without untoward results; 50 to 100 mg. per kilo daily is an average dose. In therapeutic doses aureomycin is not toxic; occasionally nausea occurs. This patient had no ill effects. It is usually given orally; we gave it intramuscularly because the child could not cooperate due to stupor.

The boy seemed to be dying. A natural cure may start between the fourteenth and eighteenth day. Though the drug was given between the eleventh and eighteenth days, I am sure it was the cause of his improvement.

DR. PHILLIPS.—Recently I took care of another case of typhus fever. This girl was severely ill for five days with typical toxicity and rash. On the sixth day the *Proteus OX19* was positive in a dilution of 1-640. Chloromycetin was then started (50 mg. per pound per twenty-four hours). The temperature rapidly came down within forty-eight hours, the child's general condition improved, her stupor rapidly disappeared, and the rash vanished quickly. On the tenth day Weil-Felix reaction was positive to 1:1,280. The drug was stopped and no complications developed.

The two cases seemed to be of equal severity but the second case treated with chloromycetin seemed to recover more quickly than the first.

ADDENDUM

DR. REILLY.—Recently a third patient with typhus fever, type Rocky Mountain spotted fever, S.E. No. 85912, came to us on the fifth day of her disease. She had a typical history and rash and was quite ill. A number of ticks had bitten her. Chloromycetin was started in the same dosage as above on the seventh day; by the tenth day the fever had left. Recovery was uneventful.

Case 2. Esophageal Atresia With Tracheoesophageal Fistula; Successful Operation

DR. JOHN A. HARREL, JR. (Assistant Resident in Pediatrics).—This female infant was born at 8 A.M. Feb. 20, 1949. The child was apparently in good condition at birth and had no trouble until twelve hours after birth when the

first feeding was attempted. She took only a small amount when she strangled and regurgitated. She had cyanotic spells following this and very thick mucus in the throat which would flow freely from the mouth. The child was then brought to our emergency room. Examination revealed a normal full-term infant who was having no respiratory difficulty but who had considerable whitish, thick mucus in throat and mouth. This was aspirated. The child was given a trial feeding of distilled water and after taking only a few swallows, regurgitated and became choked. She was then taken to x-ray and a small catheter was inserted into the esophagus; it could not be passed beyond the upper third. A small amount of Lipiodol was injected. Fluoroscopy and spot films (Fig. 1) revealed a smooth, abrupt closure of the thoracic esophagus at about the level of the carina. Filling of the bronchi did not occur. A lower esophageal segment was not visualized. An air bubble was in the stomach.

Fig. 1.—Case 2, showing a good excursion of the proximal esophageal segment.

The mother was 18 years old and the father was 21 years old. This was the first child. Total labor was nine hours. Serology was negative on both the mother and father. The mother had no illnesses during pregnancy, and had

approximately eight months' gestation. The infant's weight was 6 pounds, 9 ounces at birth.

Physical examination was quite negative. No dehydration had yet developed. Heart, lungs, and abdomen particularly were normal. There was no anemia.

Fig. 2.—Case 2. Postoperative appearance showing patent, nonleaking anastomosis.

Hydration was maintained by parental injection of lactated Ringer's solution. At the age of 36 hours, Dr. James Growden elected to do a right extrapleural approach to the esophagus. The roentgenogram showed that the dilated upper esophageal segment was capable of moving to practically the lower third of the thorax and, therefore, it was likely that an anastomosis was possible, presuming that a reasonable amount of lower segment was present.

Local anesthesia was started. A tracheal fistula just above the carina was found; the lower esophageal segment was found large enough to permit anastomosis and the dilated upper esophageal segment was found connected by serosa to the lower segment. Ether anesthesia with positive pressure was then started. The fistula was closed and the lower segment freed and anastomosed to the upper. A polyethylene catheter was placed in an ankle vein before operation and fluid and blood were given.

Postoperatively the infant did very well. A small amount of serosanguineous fluid and air had to be removed from the right thorax one day after surgery. Feedings consisted of parenteral fluids and blood through the indwelling catheter. On the fourth day a small amount of Lipiodol by mouth showed (Fig. 2) a patent, nonleaking, normally functioning anastomosis. A gastrostomy was done on that day for a feeding route and possible retrograde dilatations. Feeding was started on the fifth day. Purposefully no oral feedings were hazarded until the twelfth postoperative day. No difficulties were encountered with these oral feedings and the baby has progressed satisfactorily in all respects.

DR. REILLY.—Dr. Harrel is to be commended for his prompt recognition of an esophageal atresia and tracheoesophageal fistula.

We encountered a similar case two months before which was widely discussed. The general condition of the patient prevented exploration of chest. The most that could be done was a gastrostomy and exteriorization of upper blind esophagus, for the segments could not even have been approximated, as the autopsy confirmed.

The most common defect (in 70 to 80 per cent of cases) consists of a blind upper segment and a connection of the lower segment to the trachea just above its bifurcation. This defect has a characteristic sequence which should stay in memory, rare though it is (one in about 10,000 births): profuse mucus drooling from the mouth, vomiting the first and all subsequent feedings as soon as the few small swallows go into the esophagus, usually choking, coughing, and cyanosis with the vomiting, and the presence of bile and particularly gastric secretion. The baby may be quite all right otherwise for several days or until pneumonia and starvation set in. The excessive mucus comes from the lung due to the irritation of foreign matter such as food, bile, and gastric juice. Mucus before feeds have been taken may, therefore, indicate fistulous connection to the esophagus just as does bile in vomitus and air in the stomach. These three findings are diagnostic aids. The point where a catheter stops will help in diagnosis as well as locate the lower level of the upper segment. One should use Lipiodol rather than barium for visualization, for the latter is more irritating if it is thrown into the lung by regurgitation; it would be well to use only a bit of Lipiodol and try to aspirate that after the roentgen examination.

There are several other varieties of complete atresias which we will not consider.

The esophageal atresias can now be approached operatively and this major undertaking should be considered separately for each case. Early recognition is paramount; otherwise drowning or pneumonia could defeat any successful operative approximation of the esophageal segments. Such an approximation depends on the amount of mobility of the segments, nature of wall, and size of lower segment, which is usually sufficient in most cases, and the amount and type of tissue in the lower segment to work with. Occasionally this consists of only a thin cord impossible to anastomose. Prior roentgen visualization will give a good estimate; examination at exploration may be the only way to tell. This is justified, for the baby will surely die if denied the benefit of exploration. Most of the experienced surgeons like Haight and Towsley,[3] feel that once the diagnosis is made operation should be done as soon as dehydration or anemia is corrected. Aspiration of the extra mucus and medication for a pneumonia or other fever, if present, should be undertaken. This should require only about one day. Haight recommends a one-stage operation through an extrapleural approach, closing the fistula and anastomosing the ends of the segments.

Dr. James H. Growdon (Assistant Professor of Surgery).—The enthusiasm for surgical treatment of congenital atresia of the esophagus with tracheo-esophageal fistula was not so great until recent years, when Haight, Ladd and Gross, and others showed that primary anastomosis of esophagus within the thoracic cage was feasible in perhaps 60 to 75 per cent of cases. This results in a relatively normal situation. Methods which entailed the construction of an extra thoracic esophagus were long, tedious, and often not too satisfactory.

Once diagnosis is made, thoracotomy is indicated as early as possible to determine the feasibility of such a procedure. As Dr. Reilly has indicated, this will depend usually on the length and mobility of the upper segment and the length and size of the upper portion of the lower segment of the esophagus. The walls of the lower segment may be very thin and poorly developed. Where a primary anastomosis is not feasible, the upper segment should be brought out the lower neck in anticipation of later constructing an extrathoracic esophagus, and the fistulous connection between esophagus and trachea should be closed. A gastrostomy for feeding purposes may be performed within the next day or two.

In this case a gastrostomy has been performed for feeding purposes and will be maintained until it is ascertained when dilation of the anastomosis will be necessary in this patient. If this becomes necessary a gastrostomy will aid in passage of a thread to guide the bougies as in other esophageal strictures.

Case 3. Incomplete Rotation of Intestines With Duodenal Obstruction

Dr. William P. Barron (Assistant Resident in Pediatrics).—L. W. is a 4-month-old white female infant. She weighed 7 pounds at birth. Delivery was spontaneous and uncomplicated in the home, attended by a midwife. The infant was put on the breast and did well for the first three weeks of life, weighing 9 pounds at the end of that time. At that time she began having postcibal

vomiting which occurred fifteen or thirty minutes after a feeding. At first the vomiting occurred one or two times a day but gradually increased until it occurred after almost every feeding. The vomitus was always characteristically bile-stained.

She was taken off the breast and put on several formulas, but the vomiting persisted and the patient began to lose weight rapidly.

She was first brought into this hospital at 3 months of age.

Fig. 3.—Case 3. Note the dilated duodenum constricted (arrow) in its second and third portions.

Family History.—One child was born prematurely and died four days after birth. A 3-year-old child is apparently normal. A 2-year-old boy has been treated in the orthopedic clinic for congenital deformities of the lower extremities. The child is quite dark in color, with black, kinky hair and all the physical characteristics of a Negro, in marked contrast to his two blue-eyed, blonde sisters and parents.

On admission to the hospital, the physical examination revealed a markedly emaciated and dehydrated 3-month-old white female infant weighing 8 pounds, 6 ounces. She was quite irritable and appeared chronically ill. There was a

small umbilical hernia, the ring measuring one centimeter in diameter; there was also noted a soft mass 2.5 cm. in diameter in the right upper quadrant which moved slowly to the right with peristalsis. There were no other findings except a marked anemia.

Preoperatively she continued to vomit bile-stained vomitus fifteen to thirty minutes after eating. Her stools were fairly normal, pasty yellow or green. A gastrointestinal series (Fig. 3) revealed the swallowing function and the stomach to be normal but the duodenum was markedly dilated throughout the first portion. A constriction or partial obstruction was seen in the second and third portions of the duodenum. A barium enema showed the sigmoid to fill and extend toward the right side of the abdomen instead of to the left. There was a marked derangement of the normal pattern of the colon, and the terminal ilium was visualized in the right midabdomen.

An exploratory laparotomy was performed on the sixth hospital day after the patient's condition had been improved with whole blood transfusions and fluid administration.

Her postoperative course was uneventful and the patient began to take her formula without vomiting. She rapidly improved and gained weight and was discharged on the thirteenth postoperative day.

The mother brought the patient back to the hospital four days ago (one month postoperatively) with a history of vomiting and obstipation for the previous two days. She was slightly distended and it was thought that there may have been a complete or more probably a partial obstruction due to the other congenital adhesions. After thirty-six hours of observation she started passing gas per rectum, having bowel movements and retaining her feedings, so that it seems that the obstruction has been spontaneously relieved. A gastrointestinal series and barium enema made today showed no obstruction but there is still a narrowing at the duodenojejunal junction. The stomach was entirely empty at the end of three hours.

Dr. Reilly.—There were several important findings here: In the neonatal period vomiting of gastric contents and bile persisted for nine weeks, leading to malnutrition and the finding of a mobile mass in the right upper quadrant, which was soft and changing in size. One should think of a bowel obstruction first and other intra-abdominal lesions thereafter. The umbilical hernia, of course, was suspected but did not seem to contain bowel during the episodes. Partial obstruction was indicated by the frequent vomiting, the moderate distension, and extra peristalsis, and the fact that feces were passed. The most important localizing finding was the bilious vomitus. Pyloric stenosis as a rule does not appear so soon (3 weeks) but could, of course; if any bile is present then it is minimal. This baby vomited much bile and usually this indicates obstruction below the ampulla of Vater. Distension is usually present and this was confirmed by the roentgenogram. The most common cause is congenital bands and this is associated with failure of rotation from the left fetal position to the right-sided position of the normal full-term baby. Usually the bands are in various parts of the small intestines. Complete exploration to

cut bands and correction of the malrotation is not always as possible as some of the tests seem to indicate. The barium enema gave us much information. The barium meal localized the higher defect in the second or third portion, the part of the duodenum more commonly involved. Usually bands are found in other parts of the bowel, as we suspected. Nevertheless, exploration for any relief is to be done after attempts to correct dehydration, shock and anemia etc., are carried out.

One might diagnose a high obstruction, without x-ray visualization, by the persistent vomiting of much bile and thus not hazard further obstruction due to retention of barium. We chanced barium in order to detect a more nearly true idea of abnormal conditions in the entire bowel.

DR. G. O. DEAN (Professor of Surgery).—With the peritoneal cavity adequately exposed through a long upper right rectus incision, it became evident that malrotation of the intestines was present. Upon superficial examination the condition appeared to be identical to one type of congenital malrotation described by Ladd and Gross.[4] In their cases there were malrotation of the intestines, volvulus of the gut on the mesentery, and a constricting congenital peritoneal band extending from the right upper abdomen across the duodenum to the region of the cecum and appendix, which lay high and more or less in the midline of the peritoneal cavity just beneath the stomach.

Following the precepts of Ladd and Gross, all intestines were delivered through the incision. Then an exhaustive attempt was made to unwind the apparent volvulus, to dissect away the constricting peritoneal band, and to thereby relieve the duodenal obstruction and all obstructing mechanisms caused by volvulus, malrotation, or peritoneal bands.

However, after a period of careful dissection and cutting of all constricting peritoneal bands and thorough attention to all possibilities of unwinding the apparent volvulus, it was revealed that an additional abnormality was present in this patient. The third portion of the duodenum was being constricted by two ligamentous-like peritoneal folds which extended into and were continuous with the mesentery of the small and large bowel. The duodenum appeared to be piercing the mesentery of the bowel. The presence of a large artery and vein in each of the ligamentous peritoneal folds further complicated the relief of the duodenal constriction. In other words, there were a large artery and vein in the fold which lay in front of the duodenum and also another large artery and vein lying in the fold behind the duodenum. These two large vessels were also observed to branch profusely in the mesentery and to serve as the combined blood supply for all the small bowel and most of the large bowel. Any effort to cut one or the other of the constricting peritoneal folds would have destroyed the blood supply to approximately one-half of the intestinal tract.

It was then found that additional dissection and tugging about the vessels at the root of the mesentery would give considerable relaxation in the constricting effect on the duodenum. Shortly thereafter, gas was observed to be passing freely from the distended duodenum into the upper jejunum.

Although it was evident that the constricting effect on the duodenum might easily recur as soon as postoperative adhesions formed or in the event that even slight torsion of the mesentery should ensue, a decision was made to consider the above operative procedures as adequate to relieve the obstruction. A gastrointestinal series eight days postoperatively showed some residual duodenal dilatation and slight barium retention in the stomach at the end of six hours. Another gastrointestinal series five months later revealed a persistent narrowing of the lumen in the distal portion of the duodenum, but no retention of barium after six hours. Eight months later the patient was seen with an upper respiratory tract infection and an associated diarrhea, but she had no signs or symptoms of intestinal obstruction.

Obviously, this patient may yet develop a recurrence of the constrictive mechanism at the distal end of the duodenum. If she does develop a recurrent duodenal obstruction, the treatment of choice will be side-to-side anastomosis between the third portion of the duodenum and a proximal loop of jejunum.

Perhaps the above anastomosis should have been done during the original operative procedure. At that time it was the surgeon's impression that such an anastomosis might be indicated, but the additional time that would be required and the necessity for opening an obstructed loop of bowel were factors that motivated the surgeon to be more conservative.

In regard to the "surgical indications," several conclusions can be drawn from this case. First, after such an anomaly begins to develop the later development of blood vessels, peritoneal bands, etc., will probably deviate still further from normal and the presence of such an anomaly precludes any certainty that it can be corrected by any routine or previously formalized surgical procedures. The surgeon is beset with the necessity of carefully and prodigiously dissecting and examining all involved structures before determining his complete operative procedure. Second, the long length of time consumed during the shocking exploratory procedures may prevent the safe consummation of some indicated corrective procedures. Third, contrary to the usual description of malrotation of the intestine, this case could not be completely relieved by derotation and the cutting of constricting bands. This was borne out in our experience with three similar cases, previously explored and operated. Fourth, this and similar cases may require short-circuiting anastomosis between the duodenum and proximal jejunum.

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Psychologic Aspects of Pediatrics

EMOTIONAL DEPRIVATION IN INFANTS

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UNTIL the early years of this century, when it was the custom to keep homeless infants in institutions for custodial care, the babies quickly withered and died. Whether all perished or only most of them depended principally on one factor: the duration of their stay in the institution.

The high institutional mortality of infants was discussed at the annual meeting of the American Pediatric Society in 1915. Dr. Henry Chapin[1] reported on ten infant asylums located in different cities of the United States. In all but one institution every infant under 2 years of age died. Hamil[2] of Philadelphia, in discussing Chapin's paper, said ironically: "I had the honor to be connected with an institution in this city in which the mortality among all the infants under one year of age, when admitted to the institution and retained there for any length of time, was 100 per cent. That is, no infant admitted under one year of age lived to be two years old." Southworth,[3] speaking for conditions in New York City, said: "I can give an instance from an institution that no longer exists in which, on account of the very considerable mortality among the infants admitted, it was customary to enter the condition of every infant on the admission card as hopeless. That covered all subsequent happenings." Knox[4] described a study which he had made in Baltimore. He followed 200 infants admitted to various institutions in the city. Of these almost 90 per cent died within a year. The 10 per cent that lived, he said, did so, apparently, because, for some reason or other, the babies were taken from the institutions for short times and given into the care of foster parents or relatives.

SYMPTOMATOLOGY

Infants under 6 months of age who have been in an institution for some time present a well-defined picture. The outstanding features are listlessness, emaciation and pallor, relative immobility, quietness, unresponsiveness to stimuli like a smile or a coo, indifferent appetite, failure to gain weight properly despite the ingestion of diets which, in the home, are entirely adequate, frequent stools, poor sleep, an appearance of unhappiness, proneness to febrile episodes, absence of sucking habits.

The hospitalized infant is thin and pale but the pallor is not always associated with a reduction in the hemoglobin. The facial expression is unhappy and gives an impression of misery. Muscle tone is poor and it is possible to extend the legs fully at the knees, contrasting in this way with normal young infants. There is no alteration in the deep reflexes. The infant shows no in-

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terest in his environment, lying quietly in bed, rarely crying and moving very little. Such movements as he makes are slow and deliberate, unlike the quick movements one expects at this age. Even respiration seems quieter than in normal infants.

The appetite is indifferent and food is accepted without eagerness or interest. The weight may be stationary; there may be loss or slow gain. The amount of food necessary to effect a weight gain is much greater than in the home. Nevertheless growth in height continues at a rate only slightly less than average. The stools are frequent and, in sharp contrast to the situation in the home, it is unusual for twenty-four hours to pass without an evacuation.

Normal infants at 2 to 3 months of age smile and become animated in response to the smile or cooing voice of an attentive adult. Not so the baby who has been in a hospital for any length of time. Here it is difficult to elicit a smile in this way and repeated efforts are necessary. Sleep is light and fitful even at 3 and 4 months, resembling that of babies during the early weeks of life. Sucking habits are uncommon.

Temperature elevations, sometimes associated with mild respiratory infections, ofttimes without demonstrable cause, are frequent. We have observed babies who developed fever while in the hospital which persisted for months. We reported five infants in whom fever lasted for from three to eight months.[5] The cause of the fever was investigated with every available laboratory test but nothing was found except an occasional red throat or running ear, infections which in the home last only a day or two. There was no response to chemotherapy. In all instances the temperature fell to normal when the infants were discharged from the hospital and it remained normal thereafter.

In severe cases the symptoms are intensified and the baby assumes the appearance of a wizened, toothless old man. The cheeks are sunken, although in some instances the sucking pads in the cheeks remain; the skin is loose and somewhat inelastic; the whitish pallor is striking and the general impression is one of great weakness and frailness. The respirations are slow and superficial and often sighing.

PREDISPOSING FACTORS

The duration of hospital stay preceding the appearance of symptoms varies considerably, some children showing definite changes within a few days after entry to the hospital, others remaining for weeks without becoming ill. Age is an important factor. We have never seen the clinical manifestations of emotional deprivation during the first two weeks of life which was the usual duration of the stay for mothers and babies in obstetrical hospitals before the war. Though most babies who are born in hospitals receive very little manipulation during this time they appear vigorous, they have lusty cries and good color, and they gain well. However, if a newborn baby remains in the hospital, for one reason or another, after the first month he generally shows symptoms of hospitalism.

As a rule, prematurely born infants, especially the small ones, are unaffected by the rigid isolation practiced in the modern premature unit. Only

when they remain in the hospital for a long time and have outgrown their prematurity do they show the physical and behavioral manifestations generally associated with emotional deprivation.

A possible predisposing factor is the nature of the illness for which the child enters the hospital. It has seemed to us that children with diarrhea are more susceptible than others, possibly because this is a rather prolonged illness and one which, in itself, interferes severely with the baby's nutrition.

Another factor may be the amount of emotional satisfaction which the child had received before entry to the hospital. A certain number of babies, reared in the home, show the pallor, the quietness, and the motor retardation which are associated with emotional deprivation. Such babies are likely to be left to themselves in the hospital while the attractive, animated ones receive the affectionate attention and interest of the hospital personnel.

Infants with gross cerebral damage are not affected by emotional deprivation. Of the several hundreds of such infants who have been admitted to Bellevue Hospital in the course of years we do not recall having seen a single one who showed the clinical picture described above. Instead, they sometimes develop hyperpyrexia and die within a few days after entering a hospital. This may take place in infants who at first appear to be in excellent nutritional condition. At home they have been cared for by attentive mothers who come to understand their peculiar behavior and who cater to them. In the hospital the nurses find the mannerisms of these children strange and unpredictable and unattractive. Feeding is especially difficult and consequently the food and especially the fluid intake is inadequate. In addition they may contract infections. Presumably the hyperpyrexia is a result of dehydration, infection, and a cerebral element ("cerebral fever").

The absence of symptoms in prematurely born infants, in newborn infants, and in infants with severe cerebral damage suggests that, though the clinical manifestations of this condition in early infancy are principally physical, a certain amount of conscious cerebral functioning is necessary in order for injury to register itself.

Certain physical considerations may contribute to the speed with which babies deteriorate in hospitals. They are unable to indicate satisfactorily when they are hungry and when they have had too much, and it is hardly possible for the nurses to understand the idiosyncracies of the individual infant on short acquaintance. Moreover, the prevalent custom of prescribing food in hospitals lacks the flexibility which is possible in the home. Rigid orders for feeding are given and there is no mechanism in most hospitals whereby the infant can have more of his formula at one feeding when he is hungry and not so much at another when he is satisfied with less. Food refused at one feeding cannot be made up at another.

The rapidity with which the symptoms of hospitalism begin to disappear when an afflicted baby is placed in a good home is amazing. It is convincing evidence of the etiologic relation of the emotionally arid atmosphere of the hospital to the symptoms. The baby promptly becomes more animated and

responsive; fever, if present in the hospital, disappears in twenty-four to seventy-two hours; there is a gain in weight and an improvement in the color. A striking example was that of A.S., a boy 4 months old, who had been in the hospital for eight weeks because of diarrhea. The diarrhea ceased soon after entry but the child continued a downhill course despite all therapeutic efforts. At 4 months of age he weighed less than at birth and his condition was critical. His appearance was that of a pale, wrinkled old man. His breathing was so weak and superficial that it seemed as though he might stop breathing at any moment. When seen twenty-four hours after he had been at home he was cooing and smiling. Though no change had been made in his diet he started to gain promptly and by the end of the first year his weight was well within the normal range. He appeared to be in every way a normal child.

ETIOLOGY OF HOSPITALISM

The failure of babies to thrive in hospitals, referred to as "hospitalism," has been a matter of concern and speculation to the physician since babies were first confined in institutions. For a long time the condition was considered to be due to poor nutrition and deaths were usually attributed to malnutrition or marasmus. However, when application of the newer knowledge of nutrition failed to solve the problem of hospitalism, interest shifted to infection as the cause of the difficulty and obscure deaths in hospitals were generally listed as due to nasopharyngitis and its complications. To guard against cross-infections isolation methods were intensified. The wards for infants were partitioned off into separate little cubicles for each baby, and nurses and physicians were expected to scrub their hands and to wear gowns and masks before handling the babies. Parents were rigidly excluded except for one or two visiting hours each week. Elaborate and expensive boxes were devised, mechanically controlled, in which the babies could be cared for almost untouched by human hands. Manipulation of the babies was discouraged since handling increases the opportunity for bacterial exchange.

For many years thoughtful pediatricians have suspected that the basis for hospitalism was in some vague way related to the infant's psyche. Parrot,[6] who was associated with several foundling institutions in France, concluded that hospitalism was due to lack of adequate stimulation. Czerny,[7] felt that monotony and staring at blank walls and ceilings were important factors. Kaupe[8] emphasized the role of the mothers who could not be replaced by the most self-sacrificing nurses. The psychic and physical influence of the mother, he stated, was a very important weapon against hospitalism. A similar viewpoint was expressed by Pfaundler[9] who observed that when the mother or some sympathetic person took over the care of the child, severe damage did not take place. Even when many infants were crowded together without special attention to asepsis, that is, under unfavorable environmental conditions, if they were taken care of by their mothers (as was the case in certain foundling institutes in Austria and France), then hospitalism did not play nearly so large a part. Birk[10] held that individual care, which represents a sort of psychic contact between child and nurse, is essential for some infants, and Feer[11] believed that

lack of psychic stimulation exercises a harmful effect on the vegetative functions.

Brennemann,[12] recognizing the effect of absence of mothering, had a rule in his hospital that every baby should be picked up, carried around, amused and "mothered" several times a day. An illuminating experience is related by Dr. Fritz Talbot[13] of Boston. During a visit to the Children's Clinic in Düsseldorf some forty years ago Talbot noticed a very fat old lady wandering about the ward with a very measly baby on her hip. He asked Schlossmann, the Director, who she was and he was told that, whenever they had a baby for whom they had done everything medically and were unsuccessful, they turned the baby over to old Anna and told her to take charge. Old Anna was always successful.

Great credit is due to Dr. Henry Dwight Chapin[1] of New York who was responsible for introducing into America the system of boarding out babies in homes instead of leaving them in institutions. He was keenly aware of the need of babies for individual care and affection.

Some objective evidence of the deleterious effects of institutions on the infant's psyche was presented by Durfee and Wolf in 1933.[14] Using Buehler's tests, they compared the developmental quotients (D.Q.) of infants in various institutions and correlated their findings with the amount of maternal care which the infants received. They found that the groups of infants who had the advantage of maternal care were superior to those who did not, despite the fact that several of the institutions which restricted maternal attention were better equipped and staffed than the others. The observations of Durfee and Wolf have been confirmed and extended by the carefully controlled studies of Spitz.[15]

PATHOGENESIS

The way in which emotional deprivation registers its effects on the child is largely speculative but certain rationalizations seem justifiable. According to Rapaport,[16] the emotional process may be initiated in two ways. It may be evoked by an incoming percept from the outside or it may originate from within as, for example, when one gets excited by a novel idea, planning a trip, an anxiety. The stimulus, whether external or internal, initiates an unconscious process which mobilizes unconscious instinctual energies. The discharge process has two components, one which is physiologic and behavioral, the "emotional expression"; the other which is psychologic, the "emotion felt." These may occur simultaneously or they may succeed one another or either may occur alone.

Since young babies obviously lack the mental power to initiate emotion-producing situations, they are entirely dependent on their sensations in this respect. For the same reason the component "emotion felt" is a minor element in the emotional process as compared with "emotional expression." The physiologic and behavioral responses of the young babies to emotion-producing stimuli are not unlike those observed at later ages. Looked at from the very reason-

able viewpoint presented by Rapaport, the question as to whether the emotional responses of the newborn infant can be designated as "fear," "rage," etc., loses much of its point and the same is true for discussions regarding the ability of newborn infants to feel pleasure.[17] In a certain sense young infants may be expected to show purer emotional responses than later on since the pathways for instinctual behavior at this early age are probably wide open and not modified or blocked by cultural conflicts.

The senses—sight, hearing and equilibrium, taste, smell, the skin senses, the muscle senses, the internal sensations—are all functionally active at or shortly after birth.[18] For vision to be meaningful a certain amount of experience is necessary. Moreover, looking is an active process requiring a degree of motor control of the eye and head muscles which is attained only after several months. It is not until 4 weeks of age that the baby has progressed to the point where he will regard a dangling ring.[19] Only later, at 2 or 3 months of age does he begin to respond to a smiling face. This is not true, nearly to the same extent, of the other sensations. The newborn infant shows discriminating behavior toward sounds. He is disagreeably affected by a loud, abrupt noise and he seems pleased by a cooing voice. Sucking seems to give pleasure. Most important to the young baby appear to be the skin sensations and the kinesthetic sense. Babies are readily soothed by patting and by warmth and they cry in response to painful stimuli and to cold. The quieting effect of keeping babies outdoors may well be due, in part, to the movement of air on the skin. That the kinesthetic sense is meaningful is indicated by the soothing effect of rocking and the disagreeable effect of abrupt change in position.

Infants kept in hospitals are, as a rule, manipulated as little as possible. There are two reasons for this: inadequacy of personnel and the fear of transmitting infections. In general the more carefully run hospitals observe stricter "isolation technique" than do others. As a result the infants receive a minimum of sensory stimulation which is their only channel for initiating emotional response. It would appear that the physiologic components of the emotional process are essential for the physical well-being of the young infant and lack of emotional stimulation in early life registers its most profound effects in this sphere.

Later on psychic effects become more apparent. At 8 to 12 weeks of age, as the role of vision enlarges, the infant normally responds to a smile with a smile of his own and a show of animation. This is not the case in infants who have spent some time in an institution. Under these circumstances repeated attempts are necessary before the baby will smile. Presumably psychologic neglect leads to a blunting of the reactivity of the senses to emotion-producing stimuli. Still later, more serious and probably longer enduring psychic effects take place, as the infant begins to distinguish between the individuals in his environment and to establish relationships with them.

It is difficult to explain on the basis of infection alone the prolonged febrile episodes in hospitals and the prompt reduction in fever which takes place when the infants are returned to their homes.[5] One would hardly expect that the effects of long continued infection would disappear so promptly and constantly.

In this relation an experience with two babies who were admitted to the hospital a number of years ago for custodial care is interesting. During their first two or three months in the hospital these two babies had almost constant temperature elevations which were attributed to upper respiratory infections. Then they both seemed to make an adjustment. They remained free of fever, they gained weight, and they looked healthy and happy. At the time this happy change was attributed to the development of an immunity to ward infections. However, in retrospect, a much better explanation can be found in the fact that these two babies had become the ward favorites and, as such, they were showered with attention and affection by the nurses.

Fever of psychogenic origin has been described in a number of conditions.[20] It may be a manifestation of hysteria, it may be induced by hypnosis, it may be associated with excitement and emotional tension in the absence of physical overactivity. Its occurrence in emotionally deprived infants evades explanation at this time.

REMOTE EFFECTS ON PERSONALITY

It is not clear whether permanent damage to the psyche results if babies remain in an institution only during the first three or four months of life, but thereafter the personality distortion which takes place is, apparently, severe and long-lasting. The personality defects which result from prolonged residence in an institution during infancy have been described by Lowrey,[21] Bender,[22] and Goldfarb.[23]

According to Bender[22] behavior remains infantile, the child using such babyish devices as screaming, kicking, and temper tantrums, in response to frustration. The motor activity is often senseless and poorly patterned. The children are constantly seeking attention. Their relationships lack warmth and they readily shift their attentions from one person to another. They are unable to identify in their relationships to other people.

Language development is defective and later on the defect concerns itself with conceptualization and social concepts. At all levels behavior is impulsive, diffusely unpatterned and unmodified by motivation, discipline, punishment, or insight therapy. There is an inability to enter into and form normal relationships. According to Levy[24] lack of normal emotional response is the outstanding personality defect in the emotionally deprived child.

ANIMAL STUDIES

The ill-effects of isolation are by no means limited to the human infant. Throughout the animal world, from the minute microorganisms to the mammals, it seems to be a rule that there is safety in numbers. The deleterious influence of overcrowding has overshadowed appreciation of the protective action of companionship.[25]

Mice grow poorly when bred in solitude. Chickens raised in solitary confinement develop neurotic behavior. Colon bacilli fail to grow on agar containing gentian violet if singly inoculated on it. Only when thirty or more bacteria are used does steady and regular growth occur under these conditions. Recent

studies have shown a similar protective action of numbers of bacteria in their behavior toward media containing streptomycin.

The devices which groups use to protect themselves are varied. They have been studied by Allee and his co-workers and are summarized in his book on the *Social Life of Animals*.[25] Certain flat worms (Procerodes) die promptly when a few are placed in fresh water. With larger groups, however, the survival rate is much longer owing to the fact that the few who die give off calcium which exerts a protective action on the group. Goldfish, placed in a silver solution, protect themselves by giving off a substance which precipitates the silver. Grouped Daphnia (water fleas) survive longer than single ones when placed in an alkaline solution by excreting carbon dioxide which neutralizes the alkali. Some animals protect themselves in groups by reducing oxygen requirements. In mice the protective action of numbers seems to reside principally in better maintenance of temperature and the consequent conservation of energy and growth. An additional factor is that mice with injuries about the head can only receive treatment by licking from another individual. Isolated mice with such lesions are quickly cured by their nest mates when they are grouped.

TREATMENT

In 1941, when the thesis that the failure of babies to thrive in hospitals is due to emotional deprivation was presented before the American Pediatric Society,[26] babies were no longer dying in large numbers in institutions, as had previously been the case. The reason was that most institutions had closed their doors and were boarding their babies out in private homes instead. The problem of institutional mortality had not been solved; it had been by-passed. The clinical picture of hospitalization, however, was still frequently seen in general hospitals when babies, for one reason or another, were retained in the wards over an extended period; and in the few remaining custodial institutions.

While preparing this report it seemed appropriate to again examine emotionally deprived infants to see whether any clinical features had been overlooked. With this thought in mind I visited, together with Dr. Joseph Di Leo, a large foundling hospital which houses some 250 children, more than one-half of whom are under one year of age. I was unable to find a single baby who showed the clinical features which have come to be associated with emotional deprivation in young infants. The babies showed the motor activity and the ready response to a smile which were so rarely seen in hospitalized babies only a few years ago. The principal reason for this favorable change is the large corps of women volunteers who devote the major part of their time in the hospital to manipulating and playing with the babies.

During the last few years a wholesome change has taken place in the attitude toward the hospital care of infants in the direction of a general relaxation of the rules governing asepsis. In most institutions nurses and interns are encouraged to pick up and carry infants, and many hospitals have volunteers whose principal task it is to play with the babies. This policy has been carried out actively on the Children's Medical Services at Bellevue Hos-

pital for the past twenty years. In addition it has been the custom to assign infants who are doing poorly or who seem unhappy to particular interns for "tender loving care." This device has been well received in most instances and it has often proved as beneficial for the intern as for the baby.

An important measure for preventing hospitalism is the presence of the mother. Where it is necessary to keep a child in the hospital for any length of time as for example, in the case of subdural hematoma, the mother is invited to remain with her baby all day, if possible, and to minister to his wants. This has worked very well. The mother, instead of being a hindrance, relieves the nurses of the care of one patient and she often helps out in the care of other babies.

Contrary to what might have been expected the free manipulation of babies and the presence of parents in the ward has not increased the incidence of infections among the babies. Indeed, there has been a decrease in cross-infections. Since 1930, when an active campaign directed toward satisfying the psychologic needs of babies in the infant's ward at Bellevue Hospital was instituted, the case fatality for infants under one year fell steadily from 30 to 35 per cent to less than 10 per cent in 1938 where it has remained ever since. It is interesting to note that most of the fall in mortality had taken place before the introduction of the chemotherapeutic and antibiotic agents.

Relevant at this point is the experience at the Bassam Clinic, a surgical hospital in New Zealand, where it has been the custom to admit the mothers along with their babies requiring operations, e.g., harelip and cleft palate.[27] Each mother and child is provided with a small bed-sitting room where the mother can look after her child exactly as though she were at home. She has the companionship of other mothers in neighboring rooms and she can enjoy the garden where the babies take the air in their carriages. Surgical dressings are done aseptically, generally under light anesthesia to reduce emotional shock. The mother does all the routine work for the baby such as feeding, dressing, changing diapers, thereby saving much time for the nurses. The clinic has been running for five years and during that time there has not been a single case of cross-infection, local or general, and not a single slough or case of dehiscence.

SUMMARY

1. The failure of infants to thrive in institutions is due to emotional deprivation.

2. In young infants emotional reactions arise principally, if not entirely, in response to sensory stimuli. These stimuli set in motion processes that appear to be essential for the child's well-being.

3. To offset the adverse effects of residence in an institution, babies who require hospital care should receive manipulation, attention and affection. Whenever possible, the mother should be at the baby's bedside during the greater part of the day.

4. There is no reason to believe that more handling of the baby and the presence of the mother increase the incidence of infections; indeed, the evidence would indicate the reverse.

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Comments on Current Literature

CHEMOPROPHYLAXIS WITH CHLORAMPHENICOL (CHLOROMYCETIN) IN SCRUB TYPHUS (TSUTSUGAMUSHI DISEASE)

RAPID developments within the past two years concerning the remarkable therapeutic effectiveness of chloromycetin have borne out Smadel's original prediction that this antibiotic would prove of considerable value in the treatment of rickettsial and viral infections. Experimental studies in mice and in embryonated eggs demonstrated the effectiveness of chloromycetin against the rickettsiae of scrub typhus, epidemic and murine typhus, Rocky Mountain spotted fever, rickettsialpox and two strains of psittacosis virus. Administration of the drug to normal volunteers[1] who received maximum single or repeated oral doses showed that the toxicity was minimal. Opportunity for clinical trials in the field presented itself in the treatment of five patients with epidemic typhus.[2] The same oral doses which had been administered to human volunteers were used, and improvement was observed in all five patients with fall in pulse rate and body temperature and with no noticeable toxic effects. Subsequent opportunity for more extensive therapeutic test[3] was afforded in cooperation with the Malaya Institute of Medical Research during an outbreak of scrub typhus at Kuala Lumpur.

Continued reports of the striking effect of chloromycetin on the clinical course of epidemic and murine typhus, scrub typhus, Rocky Mountain spotted fever, of diseases caused by some of the larger viruses, and of some bacterial infections have re-emphasized the importance of this antibiotic substance. The apparent lack of toxicity, the ease of administration by the oral route, the beneficial effect even when administered relatively late in the disease, and the broad coverage of therapeutic effectiveness are outstanding features.

Chloromycetin, obtained originally from strains of *Streptomyces venezuelae* which were isolated from soil and compost,[4] has been synthesized,[5] and the synthetic product has been called chloramphenicol. Careful comparative studies[6] of the effectiveness of the two forms of the drug and preliminary clinical trials with the synthetic form indicated no essential differences. The same low level of toxicity holds true apparently for the synthetic form of chloromycetin.

Following these demonstrations of the effectiveness and minimal toxicity of chloramphenicol, it was suggested by Smadel that this synthetic form of chloromycetin, which is available in larger quantities, might prove of considerable prophylactic value. For example, in rickettsial diseases such as scrub typhus for which thus far vaccines have not been satisfactory, administration of the drug in large doses over relatively long periods might prevent the development of clinical disease in exposed persons. It seemed possible that exposed individuals protected by this means during the critical period of invasion might experience subclinical infection or develop a mild form of the disease, thereby acquiring immunity without the risk of serious rickettsial infection.

For some time Smadel and his co-workers[7] have been carrying on epidemiologic studies of scrub typhus in hyperendemic areas near Kuala Lumpur,

Malaya. In this connection opportunity for field tests of the prophylactic value of chloramphenicol was afforded.[8] Human volunteers were exposed in hyperendemic areas. One group of volunteers received chloramphenicol and a corresponding group received a placebo of calcium lactate. Both groups of volunteers were checked daily for evidence of mites of the body and for signs of illness. During the three-week period when the drug was administered, and for eight to ten days after the last dose, chloromycetin suppressed clinical evidence of infection. Following cessation of therapy, however, infection rates in persons "protected" by chloromycetin were essentially the same as those in persons who had received the placebo. With the exception of prolonged incubation period and lower incidence of eschar formation, the disease in members of the prophylactic group was indistinguishable from that in the untreated group.

Laboratory studies in mice carried on simultaneously with the studies in human volunteers showed that viable rickettsiae could be recovered regularly from the tissues of infected mice even when the animals were maintained for three months on daily doses of drug sufficient to prevent the development of clinical signs of the disease. Withdrawal of therapy resulted in infection in these treated mice, and reduction of fatalities was accomplished only by continuing the drug for at least twelve days following clinical onset. The experimental studies in animals indicated likewise that "massive inoculations of rickettsial organisms may break through the protective chemoprophylactic or chemotherapeutic effect of the drug."

The investigations in Malaya are being continued in an effort to understand more completely the process of immunity in this infection, and in the hope of working out an adequate prophylactic regime. Should such a procedure prove practicable and of general application, the prophylactic implications would be of great significance in other rickettsial infections as well as in scrub typhus.

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News and Notes

The **University of Minnesota** announces a continuation course in Pediatric Roentgenology on Oct. 31 to Nov. 5, 1949. The course, which will be presented at the Center for Continuation Study, is intended for radiologists and pediatricians. The material to be presented will include the basic medical sciences, clinical medicine, and diagnostic roentgenology, as it pertains to general and special problems in the field of childhood diseases.

Visiting physicians who will participate as members of the faculty for the course will include Dr. John Caffey, Babies Hospital, Columbia University Medical Center; Dr. Edward B. D. Neuhauser, Children's Hospital, Boston; Dr. Edith Potter, University of Chicago; and Dr. Frederic N. Silverman, Children's Hospital, Cincinnati.

A postgraduate course on the Problems of Newborn Infants, Premature and Full Term, sponsored by the **University of Colorado School of Medicine** and the **Colorado State Department of Health**, will be given at the University of Colorado Medical Center, Denver, Colo., Nov. 2, 3, 4, and 5, 1949. The guest lecturer is William L. Bradford, M.D., Associate Professor of Pediatrics, University of Rochester School of Medicine, Rochester, N. Y. Inquiries should be directed to Director, Graduate and Postgraduate Medical Education, University of Colorado School of Medicine, Denver, Colo.

Aided by a grant from the National Foundation for Infantile Paralysis, the **University of Colorado Medical Center** is offering a series of postgraduate courses on poliomyelitis. The courses are open to physicians who are graduates of medical schools approved by the American Medical Association and who reside in states west of the Mississippi. On the calendar for the school year 1949-1950, three one-week courses are scheduled: Nov. 7 to 11, inclusive, 1949; March 13 to 18, inclusive, 1950; May 22 to 27, inclusive, 1950.

Dr. Stuart S. Stevenson, formerly assistant professor of child health at Harvard University, has been appointed research professor of pediatrics at Children's Hospital of Pittsburgh and the University of Pittsburgh School of Medicine effective Sept. 1, 1949.

Dr. Alex J. Steigman is currently serving as full-time Consultant in Clinical Epidemiology for The National Foundation for Infantile Paralysis, Inc. Dr. Steigman's temporary departure from pediatrics will be for the purpose of field work in early diagnosis, management and epidemiologic investigations of poliomyelitis.

Dr. James F. Bosma of Minneapolis, assistant professor of pediatrics at University of Minnesota, has become associated with the medical staff of Elizabeth Kenny Institute in Minneapolis.

Dr. Robert H. Alway has been appointed associate professor of pediatrics at the Stanford University School of Medicine.

Dr. John W. Amesse of Denver died Aug. 21, 1949. Dr. Amesse was one of the pioneer pediatricians in Colorado and was emeritus professor of clinical pediatrics at the University of Colorado. He had always been active in the A. M. A. where he was a member of the house of delegates for many years and vice-president in 1943-1944.

Dr. Catherine S. Amatruda of New Haven died Sept. 1, 1949. She had been associated with the Yale Clinic of Child Development for a number of years, and, in collaboration with Dr. Arnold Gesell, was the author of a number of important books on child development.

Book Reviews

Clinical Endocrinology. Lawrence Martin, M.D., and Martin Hynes, M.D., Philadelphia, 1949, The Blakiston Company, 207 pages.

This book has the format of the usual "Synopsis," yet the two Cantabrigians have produced a work more critical and better documented than most books of this type. Each endocrine gland, excepting the pancreas, is discussed briefly from the standpoints of anatomy, physiology, interrelationships with other endocrines, and assay of active principles, with the bulk of the space devoted to the clinical features of dysfunction both diagnostic and therapeutic. References are given at the end of each chapter and a general index is provided. The style is good.

Much of the recent work on the adrenal is missing, and the discussions of the thymus and of childhood obesity seem inadequate. Although the book is well suited to the general practitioner, the availability in current texts of more complete discussions of the endocrine problems of childhood render it less useful to the pediatrician.

FORBES.

Prenatal Care. Publication No. 4 of Children's Bureau, Washington, D. C., 1949, Government Printing Office, 76 pages.

This is a completely rewritten edition of the pamphlet, "Prenatal Care," of which more than 9 million copies have been distributed since the first edition in 1933. The rewritten text takes cognizance of the changes in obstetrical care and our knowledge of pregnancy that have taken place in recent years. Most striking is the change from home to hospital delivery and the gradual disappearance of the midwife. The text is clear and well written for lay reading, and the material has been carefully checked and criticized by competent medical advisers. Throughout, the need for competent medical supervision is stressed during the prenatal period.

A Miniature Textbook of Feeblemindedness. Leo Kanner, M.D., New York, 1949, Child Care Publications, Child Care Monographs No. 1, 33 pages. Price $1.25.

This is a stimulating monograph which deserves wide reading by the pediatrician, who, the chances are, first has to face the question and problems of feeblemindedness in a child. Dr. Kanner discusses the inadequacy of grouping cases on the basis of organic determinants or on the degree of retardation as disclosed by mental tests, or into primary and secondary amentia, and proposes a pragmatic grouping into three divisions: absolute feeblemindedness, relative feeblemindedness, and apparent feeblemindedness or pseudofeeblemindedness. This classification, in a sense, parallels the tendency of modern psychiatry to get away from the rigid Kraepelin classification of psychoses into specific categories, and to consider the psychotic as an individual, following the influence of Freud and Meyer. The grouping proposed by Kanner would pay less attention to causes and types and look toward the study of feeblemindedness from the practical standpoint of individual, educational, communal, and medical possibilities. In the study of the individual child Kanner feels that six determinants must be evaluated: genetic, cultural, material, physical, educational, and emotional. On the basis of these six factors, a personal profile of the individual case is obtained. The importance of each determinant is discussed and illustrated from the author's experience. To the reviewer, not a psychiatrist but a pediatrician, who, over the years, has had to face many times the problem of feeblemindedness in practice and consultation, Dr. Kanner's monograph comes as a practical and common-sense ray of light in what has been a dark, dismal, and pathetic field.

B. S. V.

Editor's Column

RECOMMENDATIONS FOR THE CONTROL OF POLIOMYELITIS

THERE is no disease more upsetting to a community, to health officers, and to practicing physicians than poliomyelitis. This derives from the fact that little exact knowledge exists of how it is contracted and spread, and as a result it is difficult to give satisfactory advice on how to prevent its development in the individual or spread in the community.

As poliomyelitis has become more widespread and common in recent years, with an increasing tendency to assume epidemic proportions, some of the foolish practices that developed in the earlier epidemics have been stopped. We recall how in the epidemic of 1916 in New York some small "upstate" communities stationed police officers on the highways as they entered the village and stopped each automobile. If they carried children an officer was placed on the running board of the car and the driver forced to pass through the town without stopping. Other measures as the closing and opening of schools, theaters, and swimming pools are still matters of acrimonious discussion in many communities, and health officers become the target of panicky citizens on the one hand, and of those whose economic interests are involved on the other.

Last June the National Foundation for Infantile Paralysis called a group of nationally recognized workers in the field of poliomyelitis and in public health to a conference in Ann Arbor to discuss the subject of poliomyelitis control. Recently they have issued a memorandum on "Recommended Practices for the Control of Poliomyelitis."* No one will disagree with their findings that there is much "confusion," and that "many existing regulations require practices that are not only ineffective . . . and unwarranted by facts, but also create problems for patients and families." Based on the present limited knowledge of the disease and its epidemiology, the conference has made certain recommendations, among which the following may be singled out as attempting to answer some of the more perplexing questions that are frequently raised:

Control.—There are no preventive measures. Isolation should be for one week from the date of onset, or duration of fever, if longer. Quarantine is of no proved value.

Epidemic Measures.—Isolation of all children with fever should be made pending diagnosis. Postponement of elective nose or throat operations or dental extractions. Avoidance of excessive physical strain. Avoidance of unnecessary travel and visiting.

*Complete copies of the recommendations of the conference from which these excerpts have been selected may be obtained from the National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y.

Schools.—Public and private schools should not be closed during an outbreak, nor their opening delayed, except schools to which children are transported in busses from widely separated areas may be delayed in opening, and boarding schools should be delayed in opening if in an area where there is an outbreak of poliomyelitis.

Summer Camps may be opened if no outbreak exists in the area, but children should not be admitted from an area where an outbreak exists. When a case develops in a camp new children should not be admitted, but children in the camp should be retained for fourteen days after the last contact with the case.

Places of Recreation and Amusement, as fairs, circuses, theaters, and swimming pools, should not be closed by health officers, but the attendance of children at such places should be discouraged.

While these recommendations reflect the paucity of knowledge regarding the spread and control of poliomyelitis, their formulation by the conference gives the physician and health officer something "authoritative" to fall back on when his opinion is asked, or a decision has to be reached when poliomyelitis appears in the community.

THE ABRAHAM JACOBI MEMORIAL FUND

MANY pediatricians are unfamiliar with the Jacobi Memorial Fund which was established over twenty-five years ago by the Section on Pediatrics of the American Medical Association and named in honor of the "Father of American Pediatrics." The fund was the idea of the late Dr. Frank Neff of Kansas City, and its establishment was in large part due to his personal work and efforts. He served as custodian of the fund until his death, when he was succeeded by Dr. Hugh Dwyer. The fund is administered by the executive committee of the section and the custodian. The chief purpose of the fund when it was established was to pay the expenses of distinguished guest speakers at the section meetings. Among the guests in the early years of the fund were Findlay of England, Krasnagorski of Russia, Gorter of Holland, Finklestein of Germany, and Wallgren of Sweden. The trustees were also empowered to use the fund for pediatric purposes of national interest. Thus grants were made to landscape the Abraham Jacobi Memorial Park at Bolton Landing on Lake George, to aid in the expense of publication of the Czerny Festschrift by THE JOURNAL OF PEDIATRICS in 1933, and for a supplement to the *American Journal of Diseases of Children* on endocrine conditions. The last grant made was a contribution to the expenses of the Fifth International Pediatric Congress in 1948, in fulfillment of a pledge made a number of years earlier for a planned meeting of the Congress which was postponed on account of war.

From 1923 to 1936 many pediatricians made an annual contribution to the fund, and those contributing five dollers or more received bound copies of the Transactions of the Section until the section publications were discontinued by the American Medical Association. For some reason or other the section officers in recent years have made little use of the fund which now amounts to around five thousand dollars, although no solicitations have been made and no contributions received since 1936.

According to the minutes of the meeting of the section in Atlantic City last June, the suggestion was made that the balance remaining in the fund be turned over to a library in Chicago for the support of a pediatric division. The section unanimously voted down the suggestion. This action was correct as this disposition is not in keeping with the purposes of the contributions made by pediatricians throughout the entire country. On the other hand, it was good that attention was brought to the fund remaining idle in a bank for a number of years. If the section officers feel, as they seemingly have in recent years, that guest speakers are no longer desirable, the fund might well be gradually disposed of in grants for pediatric matters of national interest. If this is not feasible and it is found best to terminate the fund completely, we have one suggestion for consideration by the trustees. Abraham Jacobi, in whose memory the fund is named, many years ago gave from his own money to start a Jacobi Library Fund at the New York Academy of Medicine. The Academy was undoubtedly his closest professional interest, and for many years he was most active as president and trustee. The turning over of the Jacobi Fund of the section to the fund he himself started would be a solution satisfactory, we are sure, to all past contributors. However, we still feel there are a number of worthwhile things of national pediatric interest that might be aided by grants in the coming years, and it is best, as the section voted in June, not to make a final disposition of the fund at present.

COOPERATION IN RESEARCH

AN example of the value of interdepartmental research was the award of the "Silver Medal" at the scientific exhibit of the recent A.M.A. session at Atlantic City to a group from the Washington University Medical School for their exhibit on "Angiography in Congenital Heart Disease." The recipients were Drs. Moore and Scott of the department of roentgenology, Dr. Burford of the surgical staff, and Dr. Carson of the pediatric staff. The first publications of this interdepartmental group appeared in the November and December issues of THE JOURNAL OF PEDIATRICS of last year. Modern medicine has become so complex that not only has teamwork become necessary in practice, but, so far as clinical medicine is concerned, in research. Such interdepartmental teamwork, of which this is a striking example, is taking place in many of our medical schools and shows what can be accomplished by cooperation.